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INVESTIGATIONS OF BODY MASS, GASTROINTESTINAL, AND DIETARY FACTORS INFLUENCING THE EMERGENCE AND MAINTENANCE OF EATING DISORDERS

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Stockholm 2020

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Published by Karolinska Institutet.
Printed by Universitetsservice US-AB 2020

ISBN 978-91-7831-957-2

Investigations of body mass, gastrointestinal, and dietary factors influencing the emergence and maintenance of eating disorders

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To my family

ABSTRACT

Eating disorders are severe psychiatric illnesses, characterized by dysregulated eating and distorted attitudes toward weight and body shape, causing enormous suffering for patients and their families. Although great progress has been made in eating disorders research during the past decades, many questions still remain regarding the etiology and consequences of eating disorders.

The aim of this thesis was to extend the knowledge about the relationship among body mass index (BMI), gastrointestinal complaints, and diet, and how these factors contribute to the emergence and maintenance of eating disorders.

In **Study I**, we investigated the role of childhood BMI in later disordered eating behaviors across adolescence using a large, longitudinal twin cohort. BMI was reported at three time points (age 9/12, age 15, and age 18) and eating disorder symptoms were measured at two timepoints (age 15 and 18). We found a positive phenotypic correlation, meaning a correlation between BMI and eating disorders within the individual, that was stable across the ages. Further, we found a positive genetic correlation between the traits, indicating a common etiological pathway between BMI and disordered eating.

In **Study II**, we explored the effect of childhood gastrointestinal problems on later eating disorder symptoms, in the same twin cohort as in Study I. We first estimated the association in the full cohort, finding those who reported having had gastrointestinal problems in childhood scoring higher on an eating disorder symptom scale. In a second step we conditioned the analysis on twin pairs who were discordantly exposed to gastrointestinal problems during childhood, meaning that only twin pairs where one twin was affected and the other one was not contributed to the analysis. We found a decreased positive, however not null, association between gastrointestinal problems reported at age 15 and disordered eating symptoms reported at the same age, which suggests that the relationship between gastrointestinal problems and disordered eating can in part be explained by shared familial confounding factors.

In **Study III**, we evaluated the prevalence of functional gastrointestinal disorders (FGID) in different eating disorder diagnoses, as well as the association between specific eating disorder behaviors (binge eating, purging, laxative misuse, and fasting) and FGID, and lastly, we compared the total burden of FGID in individuals with high versus low current eating disorder symptoms, as well as controls. We found high prevalence of FGID in all eating disorders with up to half of the individuals with eating disorders reporting having three or more individual FGID. We found all eating disorder behaviors to be positively associated with most FGID

categories. Lastly, we found those with lower current eating disorder symptoms to have lower total burden of FGID, although still higher than healthy controls, indicating a lingering effect of gastrointestinal problems.

In **Study IV**, we aimed to explore the energy and nutrient intake in individuals with binge-type eating disorder (namely bulimia nervosa and binge-eating disorder) compared to healthy controls, and to the Nordic Nutrition Recommendations (NNR). We found women with binge-type eating disorders to have adequate intake of macronutrients (protein, fat, and carbohydrates), and most micronutrients (vitamins and minerals). However, women with binge-type eating disorders had a mean intake of energy per day that was significantly higher than controls, and higher than the recommended daily intake. In addition, women with binge-type eating disorders reported low adherence to folate, iron, vitamin D, and salt recommendations from the NNR. Although the number of men with binge-type eating disorders in the study was inadequate for statistical analysis, they did report a descriptively adequate dietary intake for most macro- and micronutrients.

The work presented in this thesis provides additional knowledge concerning the role that BMI and gastrointestinal problems play across childhood and adolescence in relation to the development of eating disorders. These insights, in combination with previous knowledge, can help develop new effective prevention strategies. This thesis also increases the understanding of the comorbidity between FGID and eating disorders, and clarifies the bidirectional relationship in the development of the two classes of disorders. Lastly, this thesis maps the energy and nutrient intake in individuals with binge-type eating disorders in relation to healthy controls, and to recommendations, and suggests a need for greater attention toward ensuring recommended daily intake of energy as well as of specific vitamins and minerals.

SAMMANFATTNING

Ätstörningar är allvarliga psykiatriska sjukdomar, som präglas av avvikande ätbeteenden och en skev uppfattning av kroppsvikt och kroppsform, och som orsakar enormt lidande för individer och deras familjer. Även om stora framsteg har gjorts inom ätstörningsforskningen de senaste årtiondena så återstår fortfarande flertalet frågor kring uppkomsten och konsekvenserna av ätstörningar.

Denna avhandlings syfte var att utöka kunskapen om förhållandena mellan BMI, mag-tarmproblematik, och kost, samt hur dessa faktorer bidrar till uppkomsten och upprätthållandet av ätstörningar.

I **Studie I** analyserade vi betydelsen av BMI under barndomen för utvecklandet av ätstörningssymptom under ungdomsåren genom att analysera data från en stor longitudinell tvillingstudie. BMI rapporterades vid tre tidpunkter (9/12, 15 och 18 års ålder) och ätstörningssymptom mättes vid två tidpunkter (15 och 18 års ålder). Våra resultat visade en positiv fenotypisk korrelation, alltså en korrelation mellan BMI och ätstörningssymptom inom individen, som var stabil över mätåldrarna. Vidare fann vi en positiv genetisk korrelation mellan BMI och ätstörningssymptom, vilket visar på ett gemensamt etiologiskt förhållande mellan de två egenskaperna.

I **Studie II** undersökte vi vilken effekt mag-tarmproblematik under barndomsåren har för senare utveckling av ätstörningssymptom, med hjälp av samma databas som i Studie I. I ett första steg beräknade vi associationen i hela populationen och fann att de som rapporterade mag-tarmproblem under barndomen också rapporterade högre symptom av ätstörningar. I nästa steg begränsade vi analysen till de tvillingpar som rapporterade att den ena haft mag-tarmproblem medan den andra inte haft det. Genom att villkora analysen och jämföra monozygota med dizygota tvillingar kan vi dra slutsatser om huruvida en potentiell association beror på ett kausalt samband mellan mag-tarmproblem och ätstörningssymptom, eller om den potentiella associationen beror på förväxlingsfaktorer med genetisk/familjär grund. Vi fann en fortsatt positiv association mellan mag-tarmproblem och ätstörningssymptom, dock svagare än i den totala populationen. Resultaten kan tolkas som att sambandet mellan faktorerna delvis kan förklaras av genetiska/familjära förväxlingsfaktorer.

I **Studie III** utvärderade vi förekomsten av funktionella mag-tarmsjukdomar i en stor fall-kontrollstudie där såväl individer med ätstörningar som friska kontroller ingick. Dessutom utvärderade vi associationen mellan olika ätstörningssymptom (hetsätning, kräkningar, överanvändning av laxermedel och fastande) och olika funktionella mag-tarmsjukdomar, och

till sist den totala bördan av funktionella mag-tarmsjukdomar hos individer med svåra respektive lätta symptom av ätstörningar, och hos kontroller. Förekomsten av funktionella mag-tarmsjukdomar var hög inom alla olika ätstörningar och upp till hälften av individerna rapporterade tre eller fler funktionella mag-tarmsjukdomar. Vi fann att alla undersökta ätstörningssymptom var positivt associerade med många av kategorierna av funktionella mag-tarmsjukdomar. Slutligen visade resultaten att de med lätta nuvarande ätstörningssymptom hade lägre total börda av funktionella mag-tarmsjukdomar jämfört med de med svåra ätstörningssymptom, dock hade de fortfarande mer funktionella mag-tarmsjukdomar än friska kontroller vilket antyder att det finns en viss långvarig effekt.

I **Studie IV** använde vi data från samma fall-kontrollstudie som i Studie III, med syftet att undersöka energi- och näringsintaget hos individer med ätstörningar med inslag av hetsätning (bulimia nervosa och hetsätningsstörning), jämfört med friska kontroller, och i förhållande till de Nordiska Näringsrekommendationerna. Resultaten visade att kvinnor med ätstörningar hade ett adekvat intag av makronutrienter (protein, fett och kolhydrater), samt av de flesta mikronutrienter (vitaminer och mineraler). Dock var det totala intaget av energi per dag högre hos individer med ätstörningar än hos kontroller, och högre än rekommendationerna. Dessutom var följsamheten till näringsrekommendationerna låga för folat, järn, D-vitamin och salt. Även om antalet deltagande män med ätstörning i studien var för litet för tillförlitliga statistiska jämförelser visade resultaten ett deskriptivt adekvat intag för majoriteten av makro- och mikronutrienter.

Sammanfattningsvis bidrar denna avhandling med ökad kunskap om vilken roll BMI och mag-tarmproblem har under barndoms- och ungdomsåren i relation till utvecklandet av ätstörningar, vilket i förlängningen kan bidra till nya preventionsstrategier. Denna avhandling ökar också förståelsen för samsjukligheten mellan funktionella mag-tarmsjukdomar och ätstörningar samt tydliggör det dubbelriktade sambandet i utvecklandet av dessa två klasser av sjukdomar. Slutligen kartlägger denna avhandling energi- och näringsintaget hos individer med ätstörningar med inslag av hetsätning i förhållande till friska kontroller och till näringsrekommendationer, och synliggör ett behov av att säkerställa ett adekvat totalt energiintag, samt intag av specifika vitaminer och mineraler.

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III. Wiklund CA, Rania M, Kuja-Halkola R, Thornton LM, Bulik CM. Evaluating Functional Gastrointestinal Disorders in Eating Disorders. *(Manuscript)*

IV. Wiklund CA, Kuja-Halkola R, Bälter K, Thornton LM, Bulik CM. Intake of energy and nutrients and adherence to the Nordic Nutrition Recommendations in women and men with binge-type eating disorders. *(Manuscript)*

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(*not included in thesis*)

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LIST OF ABBREVIATIONS

A	Additive genetic effect
AN	Anorexia nervosa
BED	Binge-eating disorder
BEGIN-SE	Binge Eating Genetics Initiative in Sweden
BMI	Body mass index
BN	Bulimia nervosa
C	Shared environmental effect
CATSS	The Childhood and Adolescent Twin Study in Sweden
C/D	Constipation and diarrhea
CI	Confidence interval
CTCT	Cross-twin cross-trait
D	Dominant genetic effect
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th ed
DZ	Dizygotic
E	Non-shared environmental effect
EDE	Eating Disorders Examination
EDE-Q	Eating Disorders Examination - Questionnaire
EDI	Eating Disorders Inventory 2
EDNOS	Eating disorders not otherwise specified
FDR	False discovery rate
FFQ	Food frequency questionnaire
FGID	Functional gastrointestinal disorders
GxE	Gene-environment interaction
GEE	Generalized estimating equations
GWAS	Genome-wide association study
HDL	High-density lipoprotein
IBS	Irritable bowel syndrome
LDSC	Linkage disequilibrium score regression
mED	Multiple eating disorders
MZ	Monozygotic

NNR	Nordic Nutrition Recommendation
OSFED	Other specified feeding or eating disorders
OR	Odds ratio
rGE	Gene-environment correlation
SD	Standard deviation
SNP	Single nucleotide polymorphism
UFED	Unspecified feeding or eating disorders

1 INTRODUCTION

Eating disorders are serious and often life-threatening mental disorders characterized by dysregulated eating and distorted attitudes towards weight and body shape. Eating disorders are associated with considerable impairment in health and quality of life and are associated with a wide range of both psychiatric and somatic comorbidities and elevated mortality.[1-5]

The etiology of eating disorders is not yet fully understood. Like all complex psychiatric conditions, eating disorders are multifactorial, and no single risk factor will fully capture their etiology. An extensive body of research has shown that eating disorders run in families,[6-9] that they are heritable,[10] and genome-wide association studies (GWAS) have begun to elucidate variants associated with anorexia nervosa.[11] In addition, emerging genetic correlations suggest both psychiatric and metabolic origins of this eating disorder.[11]

Genetic research clearly advances our understanding of the etiology of these pernicious disorders; however, genes do not act alone.[12] Given that twin-based heritability estimates hover around 40-60%, environment, including social, cultural, and individual factors, also plays a role. An unmet need in the field is understanding more about the origins of these multifaceted, often severe illnesses, and factors that contribute to their maintenance and inhibit recovery. This thesis includes four studies that extend the knowledge about the relationship among eating disorders, body mass index (BMI), gastrointestinal complaints, and diet, and how these factors contribute to the emergence and maintenance of eating disorders. In order to study the role of BMI and gastrointestinal complaints as risk factors in the development of eating disorders, we use longitudinal data from the Swedish Twin Registry enabling an exploration of the role of both genetic and environmental etiological factors. To study the relationship between gastrointestinal disorders and diet in patients with eating disorders, we rely on data from a large case-control study. This thesis provides in-depth knowledge of these complex and fundamental questions, and has the potential to inform prevention and treatment intervention of eating disorders.

2 BACKGROUND

2.1 EATING DISORDERS

Eating disorders are complex and multifactorial psychiatric illnesses characterized by dysregulated eating and in some cases, dysregulated weight. There are five main eating disorders classified according to the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-5). These include anorexia nervosa (AN), bulimia nervosa (BN), binge-eating disorder (BED), other specified feeding or eating disorders (OSFED; which contain atypical forms of the three other eating disorders, where some but not all of the diagnostic criteria are fulfilled), and unspecified feeding or eating disorders (UFED).[13] Since OSFED and UFED are not the focus of this thesis, they will not be discussed further in this text.

2.1.1 Diagnostic criteria

AN is defined as persistent restriction of energy leading to a significantly low body weight, an intense fear of gaining weight or persistent behavior that interferes with weight gain, and disturbed perception of one's body weight or shape, or persistent lack of recognition of the seriousness of the present low body weight.[13] There are two types of AN, binge-eating/purging type where recurrent episodes of binge eating and/or purging occur, and restricting type where they do not. Common to both is that negative energy balance is maintained by restricting intake and/or increasing energy expenditure.

BN is characterized by episodes of binge eating, with a binge episode defined as eating a large amount of food (by social comparison) in a short period of time accompanied by a sense of lack of control over the eating, for example feeling that one cannot stop, or cannot control what or how much one is eating. Additionally, binge eating is accompanied by recurrent inappropriate compensatory behaviors in order to prevent weight gain, for example self-induced vomiting, misuse of laxatives or other medications, or intense exercise.[13] To meet threshold diagnostic criteria in the DSM-5, both the episodes of binge eating and the inappropriate compensatory behaviors must occur, on average, at least once a week, for three months.[13]

BED is characterized by recurrent episodes of binge eating (defined in the same manner as in bulimia nervosa); however, the binge eating is not associated with recurrent inappropriate compensatory behaviors.[13] The same threshold for frequency and duration of binge episodes (at least once a week for three months) is applied to the diagnosis. BED was not a defined eating disorder diagnosis until 2013, with the release of DSM-5. Previously, it was subsumed under the general category of eating disorders not otherwise specified (EDNOS).

2.1.2 Epidemiology of eating disorders

AN commonly has its onset around puberty, but can onset at any age.[14] The lifetime prevalence of AN ranges from 0.5-3.6% for females and 0.1-0.3% for males.[6,15-19] The ranges in estimates reflects the nature of the sampled population, with estimates based on healthcare detected cases being lower than estimates from the general population.[4] In a Finnish population sample, half of the cases identified had not been detected by the health care system.[17] The female to male ratio is estimated to be 10:1 based on clinical samples.[13] However, this is most likely an underestimation of the prevalence in males as more recent evidence suggest that males comprise approximately 1 in 4 of individuals with AN.[20]

Mortality in AN is elevated compared to the general population and compared to most other psychiatric disorders. The estimated standardized mortality ratio of AN is 5.86 (95% CI, 4.17-8.26),[4,21] meaning that individuals with AN have almost 6 times higher mortality risk compared to their peers.

BN typically has its onset in older adolescence or early adulthood.[13] The lifetime prevalence of BN is estimated to be 0.5-2.8% in women and 0.1-0.5% in men.[5,6,15] The diagnosis is more common in females than males with considerable differences in estimated female to male ratios in clinical samples (10:1)[13] compared to the general population (3:1).[20] BN is also associated with increased mortality risk, with a standardized mortality ratio of 1.93 (95% CI, 1.44-2.59).[21]

BED typically has its onset in early adulthood; however, treatment-seeking patients with BED are slightly older than patients with AN and BN.[13] BED is the most common of the eating disorder diagnoses with a lifetime prevalence of 1.9-4.0% in females and 0.3-2.0% in males.[6,15,22] It is also the most common eating disorder among men and the prevalence in males has been found to be near equivalent to the prevalence in females.[23] Data on long-term outcome, including mortality, in BED are scarce. One study of 363 patients with BED reported a (non-significant) standardized mortality ratio of 1.50 (95% CI, 0.87-2.40).[24] In addition, a Finnish longitudinal follow-up study reported the all-cause mortality in BED to be 1.77 (95% CI 0.60-5.27).[25]

2.1.3 Genetics of eating disorders

The etiology of eating disorders is not fully understood. Replicated family and twin studies have shown that all eating disorders are familial and that genetic factors contribute substantially to liability.[10] Eating disorders in either parent has been shown to be independently associated with eating disorders in their female children.[26] Heritability estimates for AN range from 45-74%,[27-30] for BN from 55-62%,[31,32] and for BED from 45-57%.[7,33] Genetic effects on disordered eating become more predominant across childhood in females, specifically in the transition from early to mid-adolescence.[34] This increase has been hypothesized to be moderated by pubertal development and increasing production of ovarian hormones such as estradiol in females.[35,36] In recent years, genomics research has accelerated our understanding of eating disorders, in particular AN. The largest genome wide association study (GWAS) for AN identified 8 significant genetic regions (loci) on chromosomes 1, 2, 3, 5, 10, and 11, although it is expected that the number of significant loci will increase with increasing sample size in future studies.[11] In addition, summary statistics from GWAS have been used to calculate a number of single-nucleotide polymorphism (SNP)-based genetic correlations (using linkage disequilibrium score regression [LDSC]) between AN and a wide range of metabolic and anthropometric phenotypes. LDSC is a method to estimate the magnitude and direction of shared genetic effects between phenotypes by calculating genetic correlations.[37,38] The study found genetic correlations between AN and fasting insulin, insulin resistance, leptin, type 2 diabetes, and high-density lipoprotein (HDL) cholesterol. Give these results, the authors propose that AN should be reconceptualized as having both psychiatric and metabolic origins. Large-scale genome-wide association studies are still lacking for BN and BED; however, global efforts are ongoing.

Although these results reveal a moderate to strong genetic contribution to all eating disorders, the studies also highlight that environmental factors and/or gene environment correlations and interactions are involved and are worth exploring.

2.1.3.1 Gene x Environment correlation (rGE)

The correlation between genes and environment can be explained through three major pathways: passive, evocative, and active.[39] Passive rGE refers to the correlation between the genotype the child inheres from their parents and the environment which is provided by the same parent, in which the child is raised. One example can be eating disorders in a parent, a trait that is heritable but can also influence the environment that that same parent creates for the child (e.g., an anxious feeding environment, or a focus on weight or physical appearance) which could increase risk for developing disordered eating.[40] The genetic factor influencing eating disorder risk is then correlated with the greater likelihood of living in a disordered eating environment.

Evocative rGE describes how a genetically influenced trait evokes or induces an environmental response from others.[39] For example, an individual with a genetic predisposition to an eating disorder who is dissatisfied with their body composition may constantly seek out appearance-related reassurance from individuals in their environment, thereby creating an environment that is overly focused on appearance, which could then contribute to the emergence or maintenance of a disordered eating behavior.[40]

Active rGE refers to how a person also contributes to their environment by actively seeking circumstances that match their genotype,[41] for example a person with elevated risk for AN and associated traits like perfectionism may self-select into activities with high focus on appearance and precision (e.g., figure skating or ballet) or weight (e.g., martial arts or ski jumping).[40]

2.1.3.2 Gene x Environment interaction (GxE)

Gene-environment interaction refers to the way genes and environment affect the phenotype[42] and indexes genetic control of sensitivity to differences in the environmental response. In some cases, it is the sensitivity to risk factors of a disease that are inherited, and not the disease itself. In addition, individuals with different genotypes may react differently to the same environmental exposure.[43] One example could be the differences in risk of developing disordered eating behaviors when exposed to a weight-shaming coach between individuals with low versus high genetic susceptibility to eating disorders.

Understanding gene-environment correlations and interactions may aid in predicting disorder development and can provide information for prevention strategies. The interplay between genes and environment is a complex combination of environmental factors and contexts, the phenotype, and genetic liability. As this thesis mainly focuses on environmental factors in relation to eating disorders, it is important to bear in mind that genetic and environmental factors jointly influence risk.

2.2 BODY MASS INDEX AND WEIGHT

Like in eating disorders, genetic factors influencing BMI become more prominent from middle childhood to adulthood.[44,45] Twin- and family studies show that BMI is strongly heritable with estimates ranging from 40% in early childhood, to 75% in adulthood.[45] Moreover, GWAS studies of BMI have identified more than 500 BMI-associated loci.[46] How BMI and eating disorders are related is an important scientific topic. In general, individuals with AN are underweight, individuals with BN can be of any weight but tend to be in the normal to overweight range, and individuals with BED tend to be in the overweight to obese range, but can be of any weight ranging from normal to obese.[6] Although many argue that BMI should not even be discussed in relation to eating disorders,[47-50] others argue that BMI is central to treatment, recovery, and possibly even etiology.[51-53] The DSM-5 has also introduced a category of atypical AN, in which individuals meet all diagnostic criteria for AN except low weight.[13] The nature of this condition is hotly debated[54] as it is unclear whether individuals in large bodies who have lost a considerable amount of weight represent the same pathophysiology as individuals with classic AN.

Important insight into the relation between AN and BMI emerged from the most recent GWAS of AN, where a bidirectional, causal, relationship between AN and BMI was found, suggesting that alleles increasing the risk for AN may also increase the risk for low BMI, and correspondingly, alleles increasing the risk for low BMI may increase the risk of AN.[11] Moreover, as previously mentioned, genetic correlations between AN was also found for a number of metabolic traits. These findings suggest a shared genetic structure, independent of BMI, between AN and various metabolic phenotypes.[11] Thus, BMI should not be viewed only as a consequence of AN, but rather seen in the light of fundamentally dysregulated weight or metabolism in these individuals, and a possible explanation for the difficulty in retaining weight after treatment.

Epidemiological and clinical research on the relation between BMI and eating disorders is a well-researched topic that has yielded inconsistent results for decades. Several studies have reported elevated premorbid BMI to be a risk factor for eating disorders, especially in studies with a retrospective design.[55-59] This relationship has not been convincingly confirmed in studies with prospective designs. Research has shown elevated BMI to be positively associated,[60-62] as well as not associated[63,64] with eating disorder symptoms and behaviors. In a review on the topic, about a third of the total studies with a prospective design (*n*=31) showed elevated premorbid BMI to be associated with eating disorders.[65] The same review concluded that all included studies with retrospective designs confirmed the positive association between elevated premorbid BMI and eating disorders. Low BMI has also been shown to be both a risk and a protective factor for developing eating disorders. Some studies have shown that low weight and dieting were predictive of subthreshold and threshold AN.[66,67] In addition, studies exploring the reverse relationship found that children who engage in eating disordered behaviors are at significantly greater risk of being overweight and obese at later follow-up.[22,68]

These contradictory results from decades of previous research clearly show that well- powered, prospective, epidemiological studies investigating the underlying causes of the relationship between BMI and eating disorders are urgently needed.

2.3 GASTROINTESTINAL COMPLAINTS AND FUNCTIONAL GASTROINTESTINAL DISORDERS

In the general population, gastrointestinal problems in childhood are relatively common, with estimates ranging from 8-25% varying by sample type, nature of the problems studied, and age.[69,70] The long-term implications of childhood gastrointestinal problems are not clear, but some studies suggest that pediatric functional abdominal pain is a precursor for gastrointestinal disorders in adulthood, especially irritable bowel syndrome (IBS).[71,72] Gastrointestinal problems in childhood are often reported in other psychiatric disorders, like autism[73] and anxiety disorders.[74] Disordered eating behavior, defined as having significant problems with restrictive eating and fear of gaining weight, has also been reported to coexist with psychiatric and gastrointestinal problems in children aged 9 years.[75] Much less is known about gastrointestinal problems preceding eating disorders and their impact on the development of the illnesses. Women with BN who retrospectively reported having had problems with childhood gastrointestinal complaints, were younger when their binge-eating behavior started, and had more severe binge eating, than women with BN who did not report childhood gastrointestinal problems.[76] Previous research has also shown a positive association between celiac disease and AN, both before and after the celiac disease was diagnosed.[77] In addition, autoimmune diseases with gastrointestinal involvement, such as Crohn's disease and celiac disease have been reported to increase the risk of eating disorders in Swedish and Danish samples.[78,79]

Gastrointestinal complaints are common in individuals with eating disorders.[80-83] Problems such as constipation, bloating, nausea, and epigastric discomfort are commonly reported in AN, BN, and BED.[83-87] The extent of these problems varies across studies due to differences in screening tools, populations, eating disorder diagnosis, and setting. In addition, extensive gastrointestinal discomfort is also frequently reported during clinical renourishment of patients with AN, often contributing to premature termination of treatment.[88,89]

Longitudinal studies, evaluating gastrointestinal symptoms pre and post nutritional and/or psychological treatment, overall report improvement in most gastrointestinal conditions.[90-93] However, long-term follow-up studies evaluating gastrointestinal symptoms during recovery from disordered eating, and eating disorder symptoms during recovery from gastrointestinal disorders, are needed in order to understand the bidirectional recovery process of the gastrointestinal tract after treatment.

Functional gastrointestinal disorders

Functional gastrointestinal disorders (FGID) are disorders with chronic or recurrent gastrointestinal symptoms. They arise as a result of abnormal functioning of the gastrointestinal tract, and cannot be explained by structural or biochemical abnormalities.[94] The symptoms of FGID are related to physiological determinants including dysmotility, visceral hypersensitivity, altered mucosal immune and inflammatory function (including alterations in intestinal bacterial flora), and altered central nervous system regulation.[94]

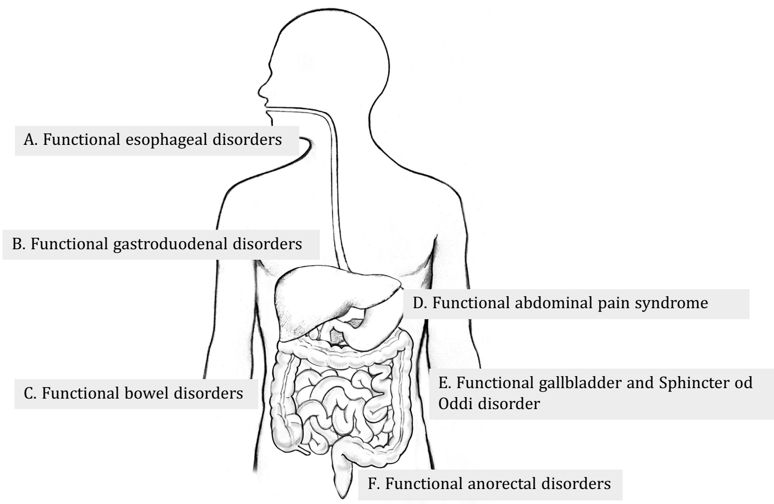

Figure 1. *Categories of Functional Gastrointestinal Disorders according to the ROME III criteria.*

Knowledge about the pathophysiology and diagnostic accuracy of FGID improved with the introduction of the ROME criteria in 1994, and FGID now have a clear taxonomy that enhances both science and clinical diagnosis and treatment.[95] Several determinants of FGID have been identified. Psychosocial factors such as stress, psychological state, and social support serve as moderators of patients' experience and behaviors and, in the end, also the clinical outcome.[95] Another closely related factor involved that influences course of illness is diet. For example, diet is the most frequently reported trigger of an episode in IBS,[96,97] and dietary restrictions are often prescribed as a part of treatment.[98] However, the relationship between FGID and eating disorders is complex and potentially bidirectional. Previous studies have found that strict dietary management may increase anxiety and concern around food, for example regarding food preparation, and in turn trigger disordered eating behavior.[99] On the other hand, poor dietary management where patients report continuing to consume triggering foods in order to promote weight loss has also been reported to be associated with disordered eating.[99]

Table 1. Full list of FGID according to ROME III criteria

ROME III Functional Gastrointestinal Disorders
A. Functional esophageal disorders A1. Functional heartburn A2. Functional chest pain of presumed esophageal origin A3. Functional dysphagia A4. Globus
B. Functional gastroduodenal disorders B1. Functional dyspepsia B1a. Postprandial distress syndrome B1b. Epigastric pain syndrome B2. Belching disorders B2a. Aerophagia B2b. Unspecified excessive belching B3. Nausea and vomiting disorders B3a. Chronic idiopathic nausea B3b. Functional vomiting B3c. Cyclic vomiting syndrome B4. Rumination syndrome in adults
C. Functional bowel disorders C1. Irritable bowel syndrome C2. Functional bloating C3. Functional constipation C4. Functional diarrhea C5. Unspecified functional bowel disorder
D. Functional abdominal pain syndrome
E. Functional gallbladder and Sphincter of Oddi (SO) disorders E1. Functional gallbladder disorder E2. Functional biliary SO disorder E3. Functional pancreatic SO disorder
F. Functional anorectal disorders F1. Functional fecal incontinence F2. Functional anorectal pain F2a. Chronic proctalgia F2b. Proctalgia fugax F3. Functional defecation disorder

Further, specific eating disorder behaviors have an impact on gastrointestinal functioning. For example, self-induced vomiting causes electrolyte disturbances such as hypokalemia, which in turn leads to constipation. In response, FGID symptoms can lead to increased somatic awareness and heightened visceral sensitivity, which is associated with increased intensity of gastrointestinal symptoms[100] and possibly leading to restriction of dietary intake.[101]

FGID are screened and diagnosed according to the ROME criteria (Table 1). In the third edition (used in Study III of this thesis) FGID are divided into six categories, depending on the site of the symptoms along the gastrointestinal tract, where each site then houses several disorders (Figure 1).

The prevalence of FGID in the general population was recently explored in a large-scale multinational study including 73 000 adults in 24 countries worldwide.[102] The study found that 40.3% of the participants reported having at least 1 FGID, that FGID were more prevalent in women than in men, and that having FGID was associated with lower quality of life and more frequent health care visits. The prevalence in children is also high and studies report estimates ranging from 10%-30% for reporting at least 1 FGID.[103,104]

To date, two studies have examined the association between the full range of FGID and eating disorders using the ROME questionnaire. Wang *et al.* compared ROME II and ROME III in two samples of patients (*n*=260) with various eating disorders (AN, BN, and EDNOS) reporting high prevalence of having at least 1 FGID in both samples (83% and 94%, respectively).[101] The most commonly reported individual FGID were postprandial distress syndrome and IBS. Boyd *et al.* investigated the stability in FGID over time in a sample of eating disorder patients (*n*=73).[105] They found FGID to be common at admission and at one-year follow-up, and there was considerable instability in what category of FGID the patients report. Both previous studies have use relatively small samples, and in addition have not included control groups, in their method limiting the possibility to further explore the results beyond describing the prevalence of the disorders in the samples. In addition, Perez *et al.* examined FGID in adolescents (mean age 15.5 years) with AN (*n*=16) using the pediatric version of the ROME III questionnaire. Individuals with AN met significantly more criteria for FGID than controls, and IBS was the most common FGID, however gastrointestinal symptoms improved after nutritional rehabilitation.[93] These results emphasize the importance of early detection, both for the improvement of eating disorder symptoms,[106] but also for recovery of gastrointestinal problems.

As mentioned, all eating disorders are associated with gastrointestinal complaints and disorders. These greatly impact on several aspects of functioning, including the quality of life in these patients.[102,107] Despite an increase in knowledge of the occurrence of these comorbidities, many of the previous studies uses small samples, and results from case studies have not been repeated in larger observational studies or clinical trials. Therefore, additional larger and controlled studies, including a control group, are necessary in order to better understand the fundamental mechanisms influencing the possible bidirectional relationship between gastrointestinal problems and eating disorders.

2.4 NUTRITION AND DIET

Despite the fact that eating is central to AN, BN, and BED, there is a surprising dearth of well-controlled large-scale nutritional studies within the field, especially in BN and BED. Eating patterns and dietary intake has been most well-studied in AN.

The dietary intake of individuals with AN has been evaluated in several studies.[41,108-119] Not surprisingly, patients with AN consume less total energy[41,108-119] and less total fat than healthy controls. Most studies report that individuals with AN have a lower intake of carbohydrates.[111,112,114,116,118,119] Misra *et al.* found patients with AN to have a higher intake of dietary fiber.[110] The literature on protein is mixed with studies reporting that patients with AN consume less[111,112,116,118,119] as well as finding no difference in the total protein consumed.[41,110] When evaluating macronutrient sources of the percentage of energy consumed, patients with AN are found to have a lower share of their energy from fat sources,[108,110,112-114,118] and higher shares coming from fibers,[108,110] and proteins,[108,114,118] along with no significant difference in the share of energy coming from carbohydrates.[108,112,114,118,119] These results converge with other findings suggesting that patients with AN experience an aversion to fat[120] and preferring low-fat food items compared to a healthy control population.[121,122]

In terms of micronutrients, patients with AN often have a lower total amount from the diet compared to the recommended daily intake; however, they are often not found to have a lower intake than the general population, most likely due to the relatively high use of supplements.[109,110,114,115] Misra *et al.* found higher total intakes of calcium, magnesium, and vitamin D in girls with AN compared to healthy controls, and in addition a large proportion of individuals with AN met recommendations for vitamin D and magnesium. However, intakes of iron, zinc, calcium, folate, and vitamin D have been reported to be low.[113,123]

A great deal of the work on dietary patterns in BN and BED has occurred in laboratory settings, with few studies exploring real-life dietary patterns in comparison to controls. Like in AN, the results are inconsistent. In laboratory settings individuals with BN and BED have consistently been found to have a higher intake of total energy compared to controls,[124-128] but with no differences in composition of macronutrient content compared to control. These results have been confirmed both when participants are instructed to simulate a binge-eating episode and when instructed to eat a normal sized meal.[129]

In observational studies, individuals with BN and BED have been found both to have a higher intake of total energy[130-133] and to not be different[134-136] when compared to BMI-matched controls. Further, studies have found the macronutrient content to be adequate and matching recommendations, and to not be different from controls.[133,135-137] Although a high daily intake of energy that is adequate in nutrient composition can result in adequate intake of vitamins and minerals, it can also lead to weight gain and increased risk of comorbidities associated with long-term exposure to high weight.[138]

Literature on micronutrient intake in BN and BED is also scarce, especially in documenting actual nutrient intake, both from diet and supplements. Individuals with BN and BED have been reported to have inadequate intakes of vitamin E, folate, magnesium, and iron.[123,137,139] However, findings are inconsistent, and there is a great need for larger, well-powered studies clarifying this important topic.

Additional research characterizing actual energy and nutritional intake as well as diet quality among individuals with binge-type eating disorders would provide valuable information that could be used to inform and develop eating disorder treatment. Nutrition counseling can and should form an important component, not only assisting patients with normalizing eating patterns, but also ensuring that their diets are optimized for long term health benefits.

2.4.1 Dietary assessment methods

The measurement of diet and nutrient intake is complex, with several methods and techniques available in epidemiological research, each one with specific advantages and limitations. Different methods are suitable for different study populations, sample sizes, and budgets. The most commonly used methods of assessment are food diaries, recall interviews, and food frequency questionnaires (FFQ).

Nutrient intake can be measured using objective or subjective methods (Table 2). Objective measures, such as food records, are a useful method in circumstances were illiteracy is high and a large portion of the food is prepared and consumed in the home. The dietary information is collected by a trained field worker who objectively observes and records all food consumed in the household across two days. The data are collected at the household level; however, individual consumption can be estimated indirectly based on age, sex, and number of individuals in the household sharing the food. Food records are not commonly used in the developed world as it is a method associated with high cost and high staff burden. Subjective measures of collecting food records are the most commonly used in epidemiological studies. The 24-hour dietary recall and dietary record methods are open-ended with the advantage of covering a large range of eating habits.

Table 2. Overview of dietary assessment methods in epidemiological studies

		Method	Time period	Type of data	Strengths	Limitations
Objective	**Food record**	Trained staff Household level Observations	Specific period (2 days)	Actual intake	Useful when literacy is low	No individual level data High cost High staff burden
Subjective	**24 h dietary recall**	Trained interviewer Open-ended questions	Past 24 hours	Actual intake	Low participant burden Cover wide range of eating habits	Dependent on respondent memory Short-term intake
	Dietary record	Self-reported Open-ended questions	Prospective (3-7 days)	Actual intake	Data recorded in real-time Cover wide range of eating habits	Respondents must be trained before participation Short-term intake
	Diet history	Trained interviewer Open-and closed-ended questions	Long period	Usual intake	Long-term intake In-depth information	Time consuming interview High cost
	Food frequency questionnaire (FFQ)	Self-reported Pre-defined questions and response options	Long period (3-12 months)	Usual intake	Low cost Suitable for large studies Useful in web-based format Long-term intake	Only records what is asked

Both methods collect short-term intake and are highly dependent on season of the year and day of the week. In the 24-hour recall method, a trained interviewer collects the data and the method is highly dependent on the respondent's memory. In the dietary record method, the respondent records the food consumed in real-time; however, disadvantages include the respondents need to be motivated and trained in the method before being able to collect the data. The diet history and FFQ methods both collect data over longer time, from months up to a year. Both methods record habitual dietary intake; however, diet history is performed by a trained interviewer while FFQ is self-report. The diet history carries a high cost as it is time-consuming both for the respondent and the interviewer, and in addition the recorded data often have to be processed and coded in food composition databases to retrieve nutrient information. The FFQ is low in cost and easy to administer and is therefore recommended for large population samples, and it is also especially well-suited for online data collection. Moreover, the FFQ carries low burden on the respondent and usually only takes approximately 15-20 min to complete. The largest disadvantage of the FFQ is that it contains close-ended questions with pre-defined frequencies, amounts, and response options, meaning there is a narrower potential range of eating habits captured.

3 AIM

3.1 OVERALL AIM

The overall aim of this thesis work was two-fold: 1) To investigate physiological factors such as BMI and gastrointestinal complaints in childhood and adolescence potentially associated with the emergence of disordered eating behaviors through genetically informative designs. 2) To explore comorbid and behavioral factors such as gastrointestinal disorders and diet influencing the maintenance of eating disorders in a clinical sample.

3.2 SPECIFIC AIMS

Study I. To explore the longitudinal genetic and environmental correlation between childhood BMI and adolescent disordered eating in a sample of young twins.

Study II. To investigate the relationship between long-term gastrointestinal complaints in childhood and disordered eating in adolescence, and to explore if the potential relationship is causal or due to familial confounding factors.

Study III. To document the prevalence of functional gastrointestinal disorders in different eating disorders subtypes, to explore how different eating disorder behaviors are associated with different functional gastrointestinal disorders, and to examine the impact of current eating disorder symptoms on functional gastrointestinal disorders.

Study IV. To evaluate the energy and nutrient intake in individuals with binge-type eating disorders compared to controls, and to further evaluate the adherence to the Nordic Nutrition Recommendations (NNR).

4 DATA SOURCES AND MEASURES

4.1 THE CHILD AND ADOLESCENT TWIN STUDY IN SWEDEN (CATSS)

The Child and Adolescent Twin Study in Sweden (CATSS) is a component of the Swedish Twin Registry[140] and is a nationwide, longitudinal study where all Swedish born twins, and their parents, are invited to participate from age 9 and continue to being followed-up during adolescence and into adulthood.[141] The study has been ongoing since July 2004, and the oldest twins in the cohort were born in 1992. CATSS twins are followed up in three waves, at age 15, at age 18, and since 2018 at age 24. For Study I and II of this thesis, we use data from the baseline and follow-up Waves 1 and 2. Although participants are invited to be included into CATSS at age 9, for the first three years of data collection (between 2004 and 2007) twins age 12 were also included. Subsequently, in the birth years 1992-1994 participating twins are 12 years old at baseline assessment. From birth year 1995 and onwards, the baseline assessment is conducted at age 9. The baseline assessment consists of a telephone interview with the parents of the twins—one separate interview per twin. The follow-up assessments are done using online questionnaires answered by both parents and children. The CATSS baseline assessment includes approximately 33 000 twins, and the overall response rate in CATSS is approximately 70%.[141,142]

When DNA from saliva is available, zygosity is determined using a panel of 48 SNPs. When DNA is not available, an algorithm based on a series of five question defining twin similarity is used to determine zygosity. The algorithm classifies more than 95% of twins correctly, according to DNA validation.[143]

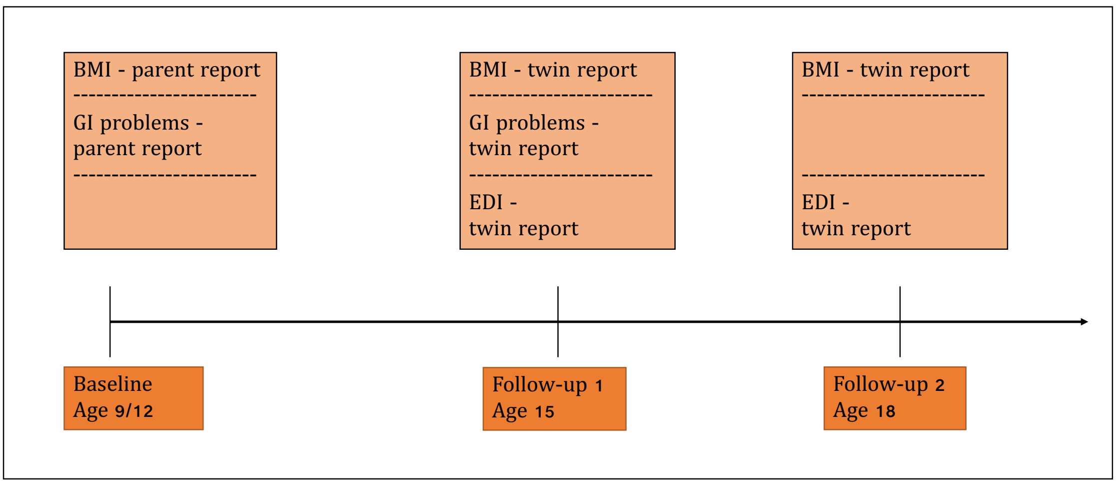

Figure 2. *Time-line of data collection in the CATSS study.*

4.1.1 Measures in CATSS

CATSS is a large-scale cohort study including multiple questionnaires and interviews. Listed below are the questionnaires and questions used in Study I and II.

Eating Disorders Inventory-2[144] (EDI)

To assess eating disorder symptoms, participants answer the Eating Disorders Inventory-2 (EDI), a well validated, self-report scale measuring different aspects of disordered eating behaviors and symptoms. The EDI produces three subscales; Drive for thinness, Bulimia, and Body dissatisfaction, and a total score, in this thesis defined as the sum of the three subscales. We analyze both the total score as well as each subscale separately. The drive for thinness subscale measures excessive concern with dieting, preoccupation with weight, and fear of gaining weight; the bulimia subscale measures binge-eating and purging episodes and behaviors; and the body dissatisfaction subscale measures dissatisfaction with one's physical appearance. Each subscale includes several items, both negatively and positively phrased, answered on a 6-point Likert scale ranging from "Always" to "Never". The EDI subscales are designed to measure core eating disorder symptoms and the scales have been validated in both clinical and non-clinical settings in Scandinavia, showing high internal reliability and the ability to distinguish between a patient- and a healthy population.[145-147] For both Study I and II, we analyzed the total score and the subscale scores as continuous variables. In the CATSS data collection, one item from the body dissatisfaction subscale is missing ("*I like the shape of my buttocks*"); however, the reverse item ("*I think my buttocks are too large*") is included. The EDI was used in the analysis in both Study I and II.

Body Mass Index

BMI [weight (kg) / height (m^2)] was calculated for all participants based on parental-reported height and weight at age 9/12 and by self-reported height and weight at ages 15 and 18. BMI is included in the analysis in Study I.

Gastrointestinal complaints

In CATSS, two categories of gastrointestinal problems are assessed: prolonged constipation and prolonged diarrhea. Parents reported these symptoms during the initial telephone interview when the twins were 9 or 12 years old. The following questions were asked and refer to the entire childhood period:

*"Does she/he have, or have ever had, problems with prolonged **constipation** growing up?"*

and

*"Does she/he have, or have ever had, problems with prolonged **diarrhea** growing up?"*

Response options are "yes" or "no". At age 15, the twins themselves answered the same questions about constipation and diarrhea, also referring to the entire childhood period. We also wanted to assess whether having more extensive problems would influence the risk of disordered eating and therefore also created a variable encompassing both problems (C/D). Those who reported having had problems with both constipation and diarrhea were scored positively, all others were scored negatively. The different gastrointestinal variables are used as the exposure measure in Study II.

4.2 THE BINGE EATING GENETICS INITIATIVE-SWEDEN (BEGIN-SE)

The Binge Eating Genetics Initiative-Sweden project (BEGIN-SE) is a large-scale, case-control study collecting genetic, intestinal microbiome, and phenotypic data in individuals primarily diagnosed with BN and BED (but also other eating disorders). Cases are identified and recruited via the National quality register for eating disorder treatment (Riksät).[148] The Riksät register is an internet-based register for individuals being treated for eating disorders and started in 1999. For individuals in the register, who were invited to participate in BEGIN-SE, the eating disorder diagnosis is determined based on a structured diagnostic interview, performed by a trained clinician. Individuals who have received a diagnosis of BN or BED in the register, and are age 18 or older are invited to participate in BEGIN-SE. The healthy control individuals participating in the study are recruited with help from a professional company from a population sample, and are frequency matched on age and sex and have no prior history, or family history, of eating disorders. In addition, the controls cannot currently be taking any medication for any other psychiatric illness. Interviewers call eligible individuals (based on matching criteria), present the study, and if the individuals are interested in participating they conduct an initial screening to determine personal eligibility. Controls who pass the screening are then contacted by data collectors from BEGIN-SE to officially be enrolled in the study. General exclusion criteria for all participation in the BEGIN-SE study are having had weight reduction surgery, having any form of inflammatory bowel disease (e.g., ulcerative colitis), current antibiotic or probiotic treatment, hormonal replacement therapy, being pregnant, or being currently breastfeeding. The first freeze of the data collected include a sample of 760 cases and 1240 controls, recruited between December 2017 and May 2020. The data from this BEGIN-SE freeze are used in Study III and IV.

4.2.1 Measures in BEGIN-SE

The BEGIN-SE study was designed to maximize information collected while minimizing participant burden. Therefore, all sampling is done in the privacy of the participants' homes and posted to the KI Biobank and all questionnaires are answered online. In BEGIN-SE each participant collects a saliva sample for genetic analysis, a stool sample for microbiome sequencing, and completes several well-validated questionnaires for deep phenotypic analysis. Questionnaires used in Study III and IV are described below.

ED100K[149]

The ED100K questionnaire is a tool to self-report lifetime eating disorders symptoms. It has been widely used in genetics studies and has been validated.[149] The ED100K shows high agreement with diagnosis determined by the structured clinical interview SCID-Module H.[150] Algorithms to classify the participants into the included eating disorders diagnosis (AN, BN, and BED) were based on DSM-5 diagnostic criteria. In addition, controls were confirmed as having no eating disordered behavior based on the ED100K as well. In addition to using the ED100K to divide participant into groups of cases, we also extracted the self-reported estimates of current, and lifetime highest and lowest, BMI. We used data from the ED100K in both Study I and II.

Eating Disorder Examination Questionnaire[151] *(EDE-Q)*

The EDE-Q is a self-report questionnaire that assesses current eating disorder symptoms and behaviors and has been translated to several languages, including Swedish.[152] The EDE-Q asks the participant to recall behaviors in the past 28 days and is therefore appropriate for classifying participants into those who are currently experiencing eating disorder symptoms or are symptom free. The EDE-Q yields four subscales (Restraint, Eating concern, Shape concern, and Weight concern) and one global score. Clinical cut-offs based on Swedish norms were used in Study III (cut-off ≥2.76 global score).[152,153] In Study IV, we used information regarding frequency of binge-eating episodes in the past 28 days in a sub-analysis of female cases.

ROME III[95]

The ROME III questionnaire is a screening tool for functional gastrointestinal disorders (FGID) in adults. There are six FGID categories (A-F) included, each referring to different part of the digestive canal, each category contains several individual FGID. The categories and individual FGID are listed in Table 1. The ROME III addresses symptoms during the past 3 months, though for some of the diagnoses there is a requirement that the symptoms should have started six months ago. In Study III we included all individual FGID, yet some disorders require clinical evaluation and/or laboratory tests to fully confirm the diagnosis.

MiniMeal-Q[154,155]

The MiniMeal-Q is a meal-based FFQ which includes 75-126 questions about food items, beverages, and dishes for assessing food habits and is used in Study IV. It is interactive and adapts the follow-up questions to only ask about the respondents' actual intake and so that the participant only has to answer questions that are relevant to them. The participants choose how often they consume different foods and dishes from a predefined list. MiniMeal-Q assesses frequencies (how many times per day/week/month) and amounts (number of drinks/slices/portions) of the different food items. For the three following food groups 1) rice, potatoes, and pasta, 2) vegetables (raw and cooked), and 3) meat, fish, chicken, and vegetarian substitutes the participants also define what portion size they normally eat on a 5-point scale, ranging from small (1) to large (5). For all other food items and dishes a standard portion size defined by the Swedish National Food Agency and the Swedish Consumer Agency is used. Based on the frequency and the amount we calculated the grams per day for all items in the FFQ.

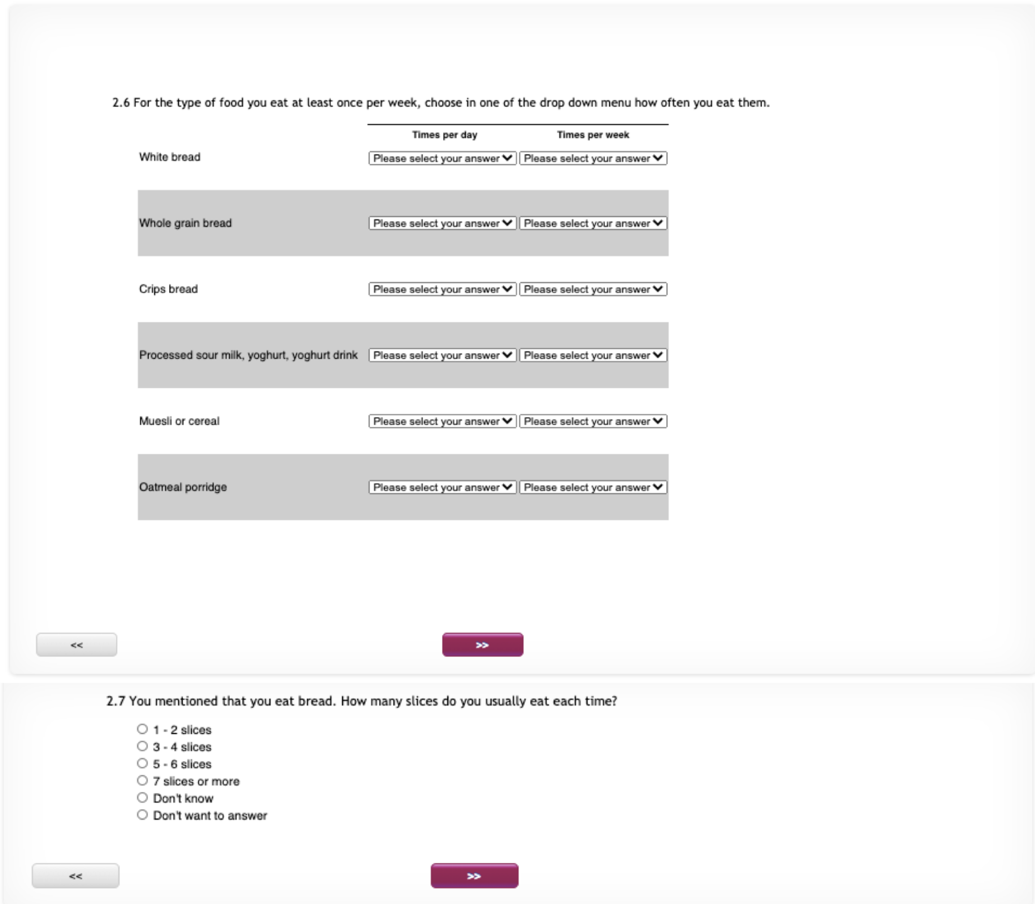

Figure 3. *Screenshot from MiniMeal-Q, from the BEGIN-SE study, translated to English.*

In the next step grams per day was linked to a Food Composition Table published by the Swedish National Food Agency (version 20191025).[156] All food items and beverages have a specific food item number in the Food Composition Table with data on energy and nutrient content for that specific food item. It is crucial to have access to an extensive, detailed, and region-specific Food Composition Table in order to attain as accurate a result as possible matching the true dietary intake. We linked the amounts calculated from the FFQ to the Food Composition Table in order to calculate daily intake of energy (kcal/day), as well as micro- and macronutrient (g/day) content for each food item. In the last step all food items in the FFQ are added together to calculate the total energy and macronutrient intake per day for the participants diet.

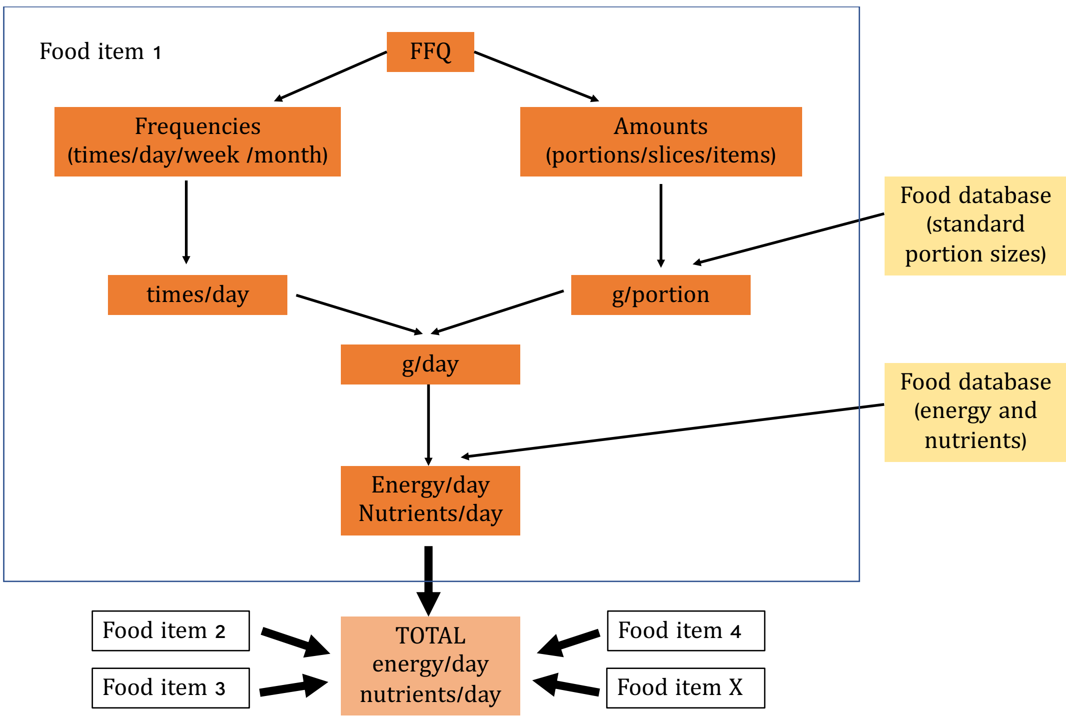

Figure 4. *Schematic picture of the nutrition calculation. Each food item (Food item 1, 2, 3, etc) is processed in several steps to calculate the energy and nutrients per day for that specific food item. All food items are then added together to reach the total energy and nutrients intake per day from the entire diet.*

Nordic Nutrition Recommendations[157]

Nordic Nutrition Recommendations, 2012 (NNR) include reference values for energy intake, recommendations for macronutrient composition expressed as a percentage of total energy intake, and recommendations for intake of fibers, salt, vitamins, and minerals.[157] Reference values are given separately for women and men. In Study IV, we compare the participants' intake of energy and nutrients with the reference values from the NNR and assess adherence to the recommendations by calculating the proportion of participants that are in the recommended range or that reached the recommended daily intake level.

5 METHODS

Table 3. Overview of studies included in thesis.

POPULATION	DATA SOURCE	MEASURES	MAIN STATISTICAL ANALYSIS
Study I: Childhood Body Mass Index and Development of Eating Disorder Traits Across Adolescence			
A cohort of Swedish twins followed from age 9/12 until age 18 (*N*=26 400)	Swedish Twin Registry: (CATSS) Interview- and web-based questionnaires to parents and twins	BMI reported at age 9/12, 15, and 18. Eating Disorders Inventory-2 (EDI) at age 15 and 18	Bivariate twin model
Study II: Prolonged Constipation and Diarrhea in Childhood and Disordered Eating Across Adolescence			
A cohort of Swedish twins followed from age 9/12 until age 18 (*N*=28 426)	Swedish Twin Registry: (CATSS) Interview and web-based questionnaires to parents and twins	Exposure: Gastrointestinal problems at age 9/12 and 15 Outcome: Eating Disorders Inventory-2 (EDI) at age 15 and 18	Within-twin pair analysis comparing the EDI score in twins discordant for the exposure. Linear regression Conditional linear regression
Study III: Evaluating Functional Gastrointestinal Disorders in Eating Disorders			
Individuals with AN, BN, and/or BED in the BEGIN-SE study. (*n*=1600, cases *n*=700, controls *n*=1200)	Binge Eating Genetics Initiative in Sweden (BEGIN-SE) Online questionnaires at one time point	ED100K for diagnosis EDE-Q for current eating disorder behavior ROME III for functional gastrointestinal disorders (FGID)	Logistic regression
Study IV: Intake of energy and nutrients and adherence to the Nordic Nutrition Recommendations in women and men with binge-type eating disorders			
Individuals with BN, and/or BED in the BEGIN-SE study. (Cases: female *n*=407, male *n*=40, controls: female controls *n*=1214, male controls *n*=13)	Binge Eating Genetics Initiative in Sweden (BEGIN-SE) Online questionnaires at one time point	ED100K for diagnosis EDE-Q for current eating disorder behavior MiniMeal-Q for diet, calculated into energy and nutrients per day	Linear regression Logistic regression

5.1 TWIN STUDIES

Twin studies are a special kind of epidemiological study used to assess and disaggregate the contribution of genetic and environmental factors to liability to a specific trait or phenotype. Twin studies are a unique tool that capitalize on the natural experiment of a population that contains identical, or monozygotic twins (MZ), and fraternal, or dizygotic twins (DZ). Twin studies allow us to estimate the relative contribution of genetic and environmental influences on liability to traits by comparing the similarity between MZ twins, who are genetically identical and share essentially 100% of their genetic material, and DZ twins, who share on average 50% of their segregating alleles, the same proportion as regular siblings.[42] If MZ twin pairs are more similar to each other in regard to a certain trait or phenotype compared to DZ twins, this implies that genetic factors play an important role in that trait or phenotype. Using this information, in combination with the assumption that all twins, both MZ and DZ, share their common environment to an equal extent, it is possible to decompose the variance in a trait or phenotype into genetic and environmental components.

5.1.1 Quantitative genetic modelling

The proportion of variance due to genetic factors in a phenotype can include both an additive effect (A) and a dominant effect (D), whereas the proportion due to environment can be further decomposed into shared environmental effect (C), meaning factors like intrauterine environment and common childhood environment, and non-shared environmental effect (E), meaning effects that are individual to the twin and contribute to differences between the twins. Measurement error is also included in E. The total phenotypic variance is equal to A+D+C+E; however, the information extracted from classical twin modelling can only estimate three out of four of these effects, and the C and D components are not commonly estimated in the same model. Usually an ACE model and an ADE model are fitted to the data separately and then compared in order to establish which model fits the data better. In order to explore the longitudinal genetic and environmental overlap between the two traits in Study I (BMI and disordered eating), a series of bivariate ACE models was used to analyze the data.

Bivariate twin model

An extension to the classic twin model is the bivariate twin model used in Study I. In a bivariate model, we estimate the relative contribution of genetic and environmental factors to the covariance between two traits. In addition to estimating the additive genetic (A), shared environmental (C), and non-shared environmental (E) effect, a series of correlation estimates can be calculated from a bivariate twin model to give information about the trait of interest.

The phenotypic correlation refers to the correlation between two traits of interest within the same individual, in Study I this would be the correlation between BMI and EDI within the same individual. The intraclass correlation is the correlation between the same trait in the same twin pair. The cross-twin cross-trait (CTCT) correlation is the correlation between trait 1 in twin 1, and trait 2 in twin 2, and vice versa. If the CTCT correlation is greater in MZ than in DZ twins, this indicates that the phenotypic correlation between the traits can at least in part be explained by common genetic factors. In addition, the bivariate heritability can be estimated. Specifically, bivariate heritability reflects the fraction of the phenotypic correlation explained by genetic factors. It is a function of the heritabilities of the two traits and their genetic correlation. In addition to calculating the additive genetic and shared and non-shared environmental effects, we can, in a bivariate model, also calculate the additive genetic and shared and non-shared environmental correlations. The additive genetic correlation is the proportion of variance that two traits share due to genetic factors; a value of 1.0 would indicate 100% overlap between the additive genetic components in each of the traits. In Study I that would mean that the genetic component of BMI would overlap to a 100% with the genetic component of EDI score. Shared and non-shared environmental correlations are defined in a similar way.

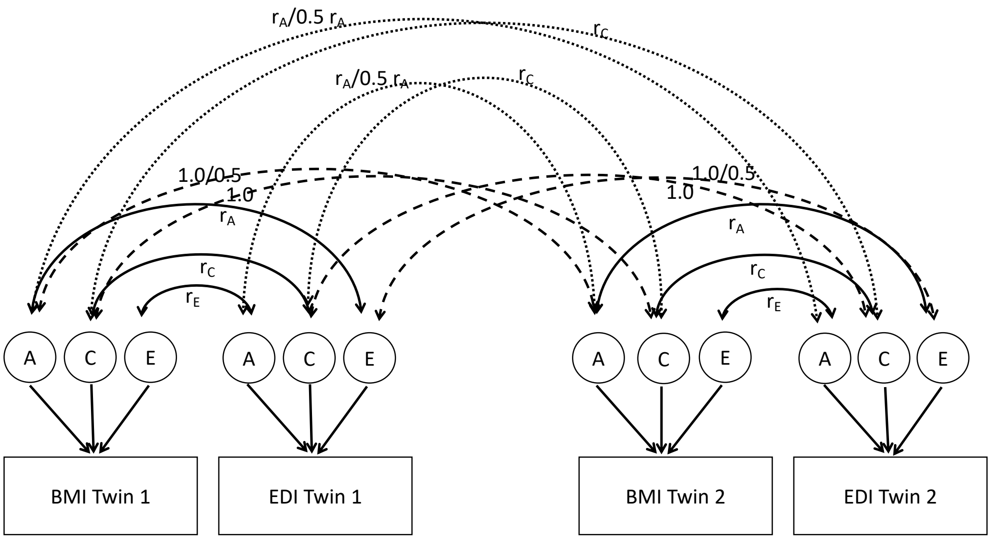

Figure 5. *Path diagram of the bivariate ACE model of BMI and EDI. The additive genetic correlation between BMI and EDI is represented by r_A, and the shared and non-shared environmental correlations are represented by r_C and r_E. The dashed double arrows indicate the correlation between Twin 1 and Twin 2 in the twin pair; additive genetic correlation is 1.0 for MZ twin and 0.5 for DZ twin, shared environmental correlation is 1.0 for both. The dotted double arrows represent the correlation between the traits between the twins, (between BMI in twin 1 and EDI in twin 2, and vice versa). The correlation is 1.0*r_A for MZ and 0.5*r_A for DZ, and correspondingly 1.0*r_C for both.*

5.2 WITHIN-TWIN PAIR ANALYSIS

In observational studies, a common strategy to adjust for confounding factors is by matching on one or several potential confounders, such as age, sex, or birthyear. By matching cases and controls on a potential confounding covariate, the distribution of the covariate is equal between cases and controls, and can thus not explain any association between exposure and outcome. In twin pairs, matching has occurred naturally for several important potential confounders since twins share both their genetic background as well as their prenatal environment. Therefore, by comparing twins where one twin is exposed and the other is not, the association cannot be explained be potential confounding factors that are stable between the twins. In other words, comparing differently exposed members of a twin pair to each other allows us to match on all the factors that the pair shares, without having to measure them. Specifically, we adjust for *unmeasured familial confounding factors*, meaning both genetic and environmental factors that are shared between the individuals in the twin pair, and that could account for a potential association between the exposure and the outcome. Examples of these factors could be shared genetic background, or environmental exposures to which twins are equally exposed. In a within-twin pair analysis, we compare DZ and MZ twin pairs, respectively, who are discordant for the exposure, thereby controlling for these familial confounding factors that are constant within the twin pair.

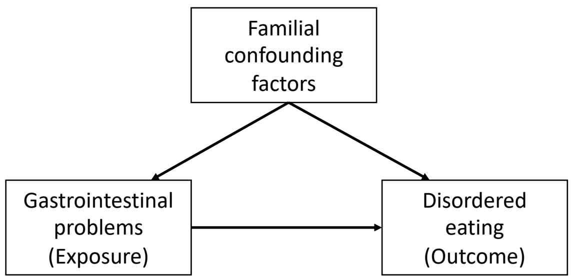

Figure 6. *Diagram illustrating familial confounding*

If the exposure and the outcome are associated solely because the exposure causes the outcome, we would expect the association to be similar in the total sample and within the twin pairs, suggesting that genetic/environmental similarities between the twins in the pair would be of no significance and would therefore not influence the association. Conversely, if the association between exposure and outcome was greater in the total sample than the association in DZ pairs, which in turn would be greater than in MZ pairs, there would be reason to assume that the association would be better explained by genetic and/or familial confounding factors.[158]

Further, we would expect no association in MZ pairs if the association were entirely due to genetic and/or familial confounding factors.

5.2.1 Conditional linear regression

When using a within-twin pair analysis design to be able to adjust for unmeasured confounding factors, we first estimate the association of the exposure on the outcome in the full population in a linear regression model. To account for the familial clustering of the twins, we use a generalized estimating equation (GEE) and a robust sandwich estimator to correct the standard errors.[159] To investigate whether genetic/familial confounding accounts for associations between the exposure and the outcome, we apply conditional linear regression models (within-twin pair analysis). Specifically, by conditioning the model on a unique twin pair identifier, we adjust for unmeasured familial confounding factors, meaning both genetic and environmental factors that are shared between the individuals in the twin pair, and that could account for a potential association between the exposure and the outcome.

5.3 CASE-CONTROL STUDIES

The aim of a case-control design is to examine if an exposure is associated with an outcome. Cases and controls are identified based on the outcome of interest (in our studies, eating disorder) where the cases have the outcome and the controls do not. Information on the exposure and covariates is then collected, often using retrospective measures such as self-report questionnaires. By definition, case-control studies are retrospective as the starting point of investigation is the outcome, and once we have the outcome we can trace back to explore the exposure. Cases and controls are often matched on variables such as age and sex to eliminate confounding and to increase efficiency.

5.3.1 Logistic regression

Logistic regression is a statistical method used when analyzing binary outcome variables, such as the outcome in case-control studies. The measure of association between the exposure and the outcome is expressed as an odds ratio (OR). An odds is defined as the ratio of the probability of an event occurring divided by the probability that the event will not occur. Thus, an OR is the odds that an outcome will occur given a certain exposure, compared to the odds that the outcome will happen when the exposure is absent. In Study III we estimate the OR of having a FGID (the outcome) given a certain disordered eating behavior (the exposure).

5.3.2 Linear regression

A linear regression model is commonly used when the outcome on interest is measured as a continuous variable. In a linear regression the relation between the exposure variable (x) and the outcome variable (y) is estimated based on a linearity assumption ($y = \beta_0 + \beta_1 x + e$).

In the model the regression coefficient is made up by the intercept (β_0) and the slope (β_1) of the relationship. The slope represents the unit increase in y, for every unit increase in x. In Study IV linear regression was used to test if there was a difference in mean intake of energy and nutrients between cases and controls.

5.4 METHODS APPLIED BY STUDY

5.4.1 Study I

Method

This study included data from the CATSS cohort, comprising twins born in Sweden between 1992 and 2007, for details on CATSS data collection see paragraph 4.1. We use the three waves of data collection at age 9/12, 15, and 18. Included were females and male twins with data on BMI at age 9/12 (*n*=26 400), age 15 (*n*=9372), and age 18 (*n*=7230) as well as EDI score at age 15 and age 18.

Statistical analysis

Means and standard deviations were calculated for the EDI total score and subscales and for BMI for the total sample and by sex.

We calculated within-trait correlations in MZ and DZ twins separately by sex and for opposite-sex DZ twins. We estimated the within-individual phenotypic correlations between BMI at ages 9/12 and 15 and EDI score at ages 15 and 18. We calculated CTCT correlations, that is, the correlation between BMI at one age in Twin 1 and EDI at a later age in Twin 2 and vice versa.

The analyses are based on standard assumptions of twin modelling. Namely, MZ twins share essentially 100% of their segregating alleles, whereas DZ twins share on average 50%, and MZ and DZ twins share their environment to an equal extent. This enables decomposition of the variance in a phenotype and the covariance between phenotypes into additive genetic (A), shared environmental (C), and nonshared environmental components (including measurement error: E). Thus, MZ twins have a correlation of 1.0 for both A and C and no correlation for E. DZ twins have a correlation of 0.5 for A, 1.0 for C, and no correlation for E.[42]

Bivariate model

We performed bivariate analyses to estimate the relative contribution of genetic and environmental factors to the covariance between BMI and EDI. Three separate models were fitted; Model 1: BMI age 9/12 and EDI age 15; Model 2: BMI age 9/12 and EDI age 18; Model 3: BMI age 15 and EDI age 18. We repeated the analysis for the three EDI subscales separately. To control for the correlated nature of BMI at different ages, we repeated the analysis including BMI as a covariate in the models. In the models, we adjusted EDI for BMI measured contemporaneously, adjusting EDI age 15 for BMI age 15 in Model 1 and EDI age 18 for BMI age 18 in Models 2 and 3.

We estimated the additive genetic, shared environmental, and nonshared environmental correlations. In addition, we estimated the bivariate heritability. As previous reports of sex differences for both BMI and EDI exist, we allowed for quantitative and qualitative sex differences in our models. Quantitative differences occur when the influence of genetic or environmental factors on the phenotype differs in magnitude between sexes. This is modelled by allowing estimates of A, C, and E to be different in females and males. Qualitative differences arise when the genetic effect on a phenotype is different between sexes. We accounted for such differences by estimating the fraction of the A correlation between females and males in opposite-sexed pairs, compared with same-sexed pairs, varying from 0 to 1.[160]

To not introduce bias and to be able to compare estimates between models and time points, we fit full bivariate models.[161] All analyses were conducted using R[162] version 3.2.2 software and statistical package OpenMx 2.7.11.[163]

5.4.2 Study II

Method

Study participants in Study II were from the CATSS cohort, same as in Study I, for details about the CATSS cohort see paragraph 4.1. The sample consisted of female and male twins born in 1992 to 2007 with information on the exposure variable (gastrointestinal problems) at ages 9/12 (*n*=28426) and 15 (*n*=8938) and outcome variable (EDI total score) at ages 15 and 18.

Statistical analysis

In all models, gastrointestinal problems were considered the exposure and disordered eating was considered the outcome. We fitted linear regression models to estimate the association between gastrointestinal problems and EDI total score using GEE methods and a robust sandwich estimator to account for the non-independent data.

To explore the significance of genetic/familiar confounding on the association between gastrointestinal problems and disordered eating, we applied within-twin pair analysis (conditional linear regression). The associations between the different EDI subscales and self-rated gastrointestinal problems at age 15 were also explored using these methods.

Because of the difficulty in determining the temporality of a potential association, we performed a sensitivity analysis between gastrointestinal problems at age 15 and total EDI score at age 18 adjusting for total EDI score at age 15.

We considered the adjusted models between constipation, diarrhea, and C/D on total EDI score (i.e., 10 tests) the primary analyses of the study. We therefore set the statistical significance threshold at $p<0.005$ to adjust for multiple comparisons. All analyses were done using R version 3.2.2[162] using the package drgee.[164]

5.4.3 Study III

Method

Participants in Study III were participants in the BEGIN-SE study, for details see paragraph 4.2. We included 760 cases and 1240 controls, recruited between December 2017 and February 2020. The ED100K was used to classify cases into groups based on lifetime eating disorders diagnosis (AN, n=305 and BN, n=188), as well as those reported having had multiple eating disorders (mED) diagnosis (AN, BN, and/or BED) in their lifetime (n=267).

The outcome in this study was FGID (both categories and individual) from the ROME III questionnaire.

Additionally, participants reported on frequency of disordered eating behaviors (binge eating, purging [self-induced vomiting], laxative misuse, and fasting) in the EDE-Q. The behaviors were coded into binary variables, those reporting binge eating, purging, and laxative misuse ≥4 times in the 28 days, as well as those reporting fasting ≥6-12 times in the past 28 days, were coded as having the behavior, those reporting a lower frequency or no current behaviors were coded as low frequency.

Statistical analysis

Prevalence of the general FGID categories, of each individual FGID, and the mean number of total FGID diagnoses across eating disorder subtypes and for controls was calculated. We compared eating disorder subtypes and controls on proportions (FGID categories) using χ^2 tests, and on continuous variables (e.g., descriptive, mean number of FGID diagnoses) using ANOVA with post-hoc tests (Tukey's HSD).

Participants reported on frequency of disordered eating behaviors (binge eating, purging [self-induced vomiting], laxative misuse, and fasting) in the EDE-Q. The behaviors were coded into binary variables, those reporting binge eating, purging, and laxative misuse ≥4 times in the 28 days, as well as those reporting fasting ≥6-12 times in the past 28 days, were coded as having the behavior, those reporting a lower frequency were coded as not having the behavior. We used logistic regression models to evaluate the association between different disordered eating behaviors and general FGID categories as well as individual FGID. In all models, disordered eating behavior was the exposure and FGID was the outcome. For functional gastroduodenal disorders (category B), estimates are provided with and without the inclusion of the cyclic vomiting symptom, given that this could be conflated with self-induced vomiting associated with eating disorders. OR and 95% confidence intervals (CI) for the crude model as well as for the model adjusted for age, sex, and BMI are presented.

The EDE-Q also yields 4 subscales and a global score. We used the Swedish norms for the EDE-Q to categorize the cases by applying a cut-off of 2.76 EDE-Q for the global score.[152] The cut-off was used to identify individuals who were currently experiencing high levels of eating disorder symptoms (i.e., reported purging, binge eating, laxative abuse, or fasting in the past 28 days) versus individuals who were currently having low levels of symptoms. We compared the mean number of FGID in each of the eating disorder groups by symptom status (i.e., high or low current symptom levels) by using a nonparametric Kruskal-Wallis test, followed by the Dunn post hoc method.

To correct for multiple comparisons, we applied False discovery rate (FDR) procedure, *q*-values (i.e., *p*-values adjusted by FDR).[165,166] All statistical analyses were performed using statistical software R, version 3.6.2.[162]

5.4.4 Study IV

Method

In Study IV, participants were again participants in the BEGIN-SE study, for details see paragraph 4.2. We included 465 cases with binge-type eating disorders and 1240 controls, recruited between December 2017 and February 2020. We used the ED100K to classify cases who reported having had a BN and/or BED diagnosis in their lifetime.

Statistical analysis

Participants with missing nutrient data or unreasonable energy intakes were excluded from the analysis (<800 kcal/day or >8000 kcal/day), n=56. The final analysis included 1621 female participants (cases: n=407, controls: n=1214) and 53 male participants (cases: n=40, controls: n=13). Means and standard deviations (*SD*) were calculated for total energy, macronutrients, as well as micronutrients. We calculated the proportion of cases and controls that reached the recommended intake levels according to the NNR for all micro- and macronutrients. Statistical analysis was only performed in women and not in men, due to the small sample of male participants. Differences in baseline characteristics between female cases and controls were tested using Student's t-test. To examine potential differences in dietary intake between female cases and controls we used linear regression models, adjusted for age and BMI in the analysis of energy and macronutrients, and age and total energy intake in the analysis of micronutrients. To analyze the differences between proportions of females adhering to the NNR logistic regression models, adjusted for age and BMI were used.

We also performed a sensitivity analysis to compare the total energy and macronutrient intake in female cases with differences in current frequency of binge eating in past 28 days, according to the EDE-Q. We divided the cases into four groups: 1) No binge-eating episodes; 2) 1-4 binge-eating episodes; 3) 5-10 binge-eating episodes; and 4) More than 10 binge-eating episodes. We analyzed intake using linear regression adjusted for age and BMI. The group with no reported binge-eating episodes in the past 28 day was used as the reference group.

To correct for multiple testing when analyzing group differences in energy and micro- and macronutrient intake, FDR was applied and q-values are presented.[165,166] Significance level q=0.05 was used. All statistical analyses were conducted using R, version 3.6.2.[162]

6 RESULTS

The results section comprises a summary of the most important results in each of the four studies.

6.1 BMI AND EATING DISORDERS

6.1.1 BMI in childhood and adolescence and development of disordered eating behavior (Study I)

Objective

The objective of this study was to enhance the understanding of the role that premorbid BMI has in the emergence of eating disorders. We explored relations between BMI and disordered eating in a longitudinal sample of young twins.

Main results

We found the positive phenotypic correlation between childhood and adolescent BMI and later disordered eating (measured by the EDI) in adolescence and young adulthood to be statistically significant over all ages in this longitudinal sample (Table 4). The correlations remained significant, although slightly lower, after controlling for BMI at the later timepoint, measured simultaneously as EDI.

Table 4. Phenotypic correlation estimates and 95% confidence intervals (CI) from the full bivariate models for BMI and EDI.

			Phenotypic correlation (95% CI)	
			Crude	**Adjusted**
Model 1	BMI 9/12 – EDI 15	Females	0.31 (0.28; 0.35)	0.13 (0.07; 0.19) *
		Males	0.29 (0.25; 0.32)	0.11 (0.06; 0.16) *
Model 2	BMI 9/12 – EDI 18	Females	0.30 (0.26; 0.33)	0.08 (0.02; 0.14) [§]
		Males	0.26 (0.22; 0.30)	0.08 (0.01; 0.15) [§]
Model 3	BMI 15 – EDI 18	Females	0.33 (0.29; 0.37)	0.08 (0.02; 0.14) [§]
		Males	0.28 (0.22; 0.33)	0.08 (0.01; 0.15) [§]

*Note: * EDI at age 15 adjusted for BMI at age 15, [§] EDI at age 18 adjusted for BMI at age 18, BMI: Body mass index, EDI: Eating Disorders Inventory-2*

We also found significant positive genetic correlations between BMI at younger ages and EDI scores in later adolescence (Table 5). The genetic correlation between BMI age 9/12 and EDI age 15 remained significant after controlling for BMI at age 15. These results add to our understanding of common etiological pathways between BMI and eating disorders traits by highlighting a common genetic effect (i.e., significant genetic correlations) between these two traits in a longitudinal model, which suggests that some of the same genetic factors play a causal role for both BMI and eating disorder traits. That is, elevated, premorbid BMI may be a risk factor for later disordered eating.

Table 5. Genetic correlation and 95% confidence intervals (CI) from the full bivariate models for BMI and EDI.

			Genetic correlation r_A (95% CI)	
			Crude	**Adjusted**
Model 1	BMI 9/12 – EDI 15	Females	0.48 (0.32; 0.65)	0.29 (0.13; 0.44) *
		Males	0.43 (0.31; 0.55)	0.23 (0.04; 0.42) *
Model 2	BMI 9/12 – EDI 18	Females	0.29 (0.16; 0.42)	0.13 (-0.01; 0.28) §
		Males	0.42 (0.26; .58)	0.25 (0.06; 0.45) §
Model 3	BMI 15 – EDI 18	Females	0.38 (0.27; .49)	0.11 (-0.02; 0.25) §
		Males	0.36 (0.23; .49)	0.09 (-0.08; 0.25) §

*Note: * EDI at age 15 adjusted for BMI at age 15, § EDI at age 18 adjusted for BMI at age 18, BMI: Body mass index, EDI: Eating Disorders Inventory-2*

6.1.2 Gastrointestinal problems in childhood and adolescence and development of eating disorder symptoms (Study II)

Objective

In the second study of this thesis, we evaluated the longitudinal associations between two common gastrointestinal problems (i.e., prolonged constipation and prolonged diarrhea) during childhood and eating disorders symptoms (measured by the EDI) in adolescence using a large longitudinal, population-based twin sample. Further we explored whether these associations are potentially causal or more likely to reflect familial confounding in a within-twin pair analysis.

Main results

In the full sample, using linear regression models, we found positive associations between both constipation and diarrhea at age 15 and EDI total score at age 15 (Table 6).

Table 6. Results from regression analyses (regression coefficients, with 95% confidence intervals (CI)) evaluating associations between EDI total score at age 15 and constipation, diarrhea, and reporting both gastrointestinal conditions (C/D) at ages 9/12 and 15 in CATSS. Models adjusted for sex.

	EDI total score 15	**EDI total score 18**
	Adjusted regression coefficient (95% CI)	**Adjusted regression coefficient (95% CI)**
Constipation age 9/12 (parent)	-0.05 (-1.57; 1.47)	1.97 (-0.09; 4.02)
Diarrhea age 9/12 (parent)	1.55 (-0.84; 3.94)	0.43 (-2.51; 3.38)
Constipation age 15 (self)	5.55 (3.77; 7.33) *	5.04 (1.97; 8.10) *
Diarrhea age 15 (self)	5.15 (2.74; 7.55) *	1.43 (-2.76; 5.63)
C/D age 15 (self)	9.52 (4.27; 14.75) *	5.58 (-2.41; 13.57)

*Note: * Indicate statistical significances at p<0.005. CI= confidence interval, EDI= Eating Disorders Inventory-2, C/D= reporting both constipation and diarrhea, self = self-report, parent = parent*

The estimated adjusted regression coefficients were 5.55 (95% CI: 3.77; 7.33) and 5.15 (95% CI: 2.74; 7.55), respectively. This means that those who reported having had prolonged constipation or diarrhea scored about 5 points higher on the EDI total scale compared to the unexposed group. Further, reporting having had both gastrointestinal conditions (C/D) during their upbringing at age 15 was also strongly positively associated with a significantly higher

EDI total score (regression coefficient: 9.52, 95% CI: 4.27; 14.75) compared to the unexposed group. Constipation at age 15 was also significantly associated with EDI total score at age 18 (regression coefficient: 5.04, 95% CI: 1.79; 8.10), however associations of diarrhea and C/D conditions at age 15 with EDI total score at age 18 were lower than at age 15, and not statistically significant.

In the within-twin pair analysis of constipation and EDI total score, (both at age 15), we found lower, but not null, estimates for both DZ and MZ twin pairs (DZ regression coefficient: 2.12, 95% CI: −0.78; 5.03 and MZ regression coefficient: 4.53, 95% CI: 0.68; 8.39) compared with the full sample estimates; however, these were not statistically significant at $p<0.005$ (Table 7).

Table 7. Results from regression analyses (regression coefficients, with 95% confidence intervals (CI)) evaluating associations between EDI total score at age 15 and constipation, diarrhea, and reporting both gastrointestinal conditions (C/D) at ages 9/12 and 15 in within pair models (DZ and MZ twin).

	EDI total score 15		**EDI total score 18**	
	Within DZ pairs§ (95% CI)	**Within MZ pairs (95% CI)**	**Within DZ pairs§ (95% CI)**	**Within MZ pairs (95% CI)**
Constipation age 9/12 (parent)	-2.0 (-4.2; 0.2) [*n*= 683]	1.1 (-2.6; 4.8) [*n*= 473]	.0.3 (-3.5; 2.9) [*n*= 473]	2.07 (-1.7; 5.8) [*n*= 135]
Diarrhea age 9/12 (parent)	1.3 (-2.6; 5.1) [*n*= 270]	-5.00 (-9.64; -0.36) [*n*= 211]	-1.13 (-6.49; 4.23) [*n*= 211]	1.38 (-4.60; 7.35) [*n*= 42]
Constipation age 15 (self)	2.1 (-0.8; 5.0) [N= 493]	4.5 (0.7; 8.4) [N= 185]	1.1 (-4.5; 6.8) [N= 185]	1.7 (-4.9; 8.3) [*n*= 65]
Diarrhea age 15 (self)	2.7 (-1.9; 7.2) [*n*= 173]	0.3 (-5.2; 5.8) [*n*= 65]	-0.6 (-8.2; 9.3) [*n*= 65]	-2.4 (-9.0; 4.2) [*n*= 42]
C/D age 15 (self)	5.6 (-1.9; 13.1) [*n*= 71]	4.5 (-4.0; 13.0) [*n*= 17]	6.6 (-8.2; 21.4) [*n*= 17]	-3.8 (-18.4; 10.7) [*n*= 13]

Note: n= Number of individuals from exposure discordant twin pairs in analysis, DZ= dizygotic, MZ= monozygotic, EDI= Eating Disorders Inventory-2, C/D= reporting both constipation and diarrhea, self = self-report, parent = parent § Adjusted for sex

This can be interpreted as constipation having a strong association with EDI total score at age 15, and that the association is partly explained by familial/genetic factors. In the within-twin pair analysis of constipation at age 15 and EDI total score at age 18, estimates were low and not statistically significant.

No statistically significant association was found between diarrhea and EDI total score at age 15 in the within-twin pair analysis. The interpretation is therefore that the previously observed association between the exposure and outcome can largely be explained by familial (genetic and/or environmental) confounding. The within-twin pair analysis for diarrhea at age 15 and EDI total score at age 18 did not show any significant associations either; however, the confidence intervals were very wide, most likely due to small number of exposure discordant twins (DZ: *n*=65, MZ: *n*=42). Associations between C/D conditions and EDI total score at age 15 were not statistically significant.

6.1.3 Evaluating functional gastrointestinal disorders in eating disorders (Study III)

Objective

The objective of this study was to comprehensively evaluate the prevalence of FGID in a large sample of individuals with several eating disorder diagnoses in comparison to controls. We also examined the specific impact of disordered eating behaviors, such as binge eating, purging, misuse of laxatives, and fasting, on the risk for developing problems in specific FGID categories. Lastly, we compared the total number of FGID in individuals reporting high vs. low current eating disorder symptoms (as measured by the EDE-Q), and with healthy controls.

Main results

FGID were widespread across eating disorder groups and in healthy controls: 92% of cases and ~80% of controls reported having at least one individual FGID (Table 8).

Table 8. Prevalence (%) of functional gastrointestinal disorders (FGID) categories in eating disorder cases, and controls.

FGID	**Cases**			**Controls**	
	AN (*n* = 305)	*BN* (*n* = 188)	*mED* (*n* = 267)	*HC* (*n* = 1240)	q<0.05
A. Functional esophageal disorders	**19.0**	**26.6**	**30.7**	**9.4**	HC<AN<BN/mED
B. Functional gastroduodenal disorders	**32.1**	**41.5**	**45.7**	**7.5**	HC<AN<BN/mED
C. Functional bowel disorder	**85.9**	**92.6**	**92.1**	**78.8**	HC<AN<BN/mED
D. Functional abdominal pain syndrome	**-**	**-**	**-**	**-**	
E. Functional gallbladder and Sphincter of Oddi (SO) disorders§	**-**	**-**	**-**	**-**	
F. Functional anorectal disorder	**16.4**	**23.4**	**27.3**	**9.0**	HC<AN<BN/mED
At least 1 FGID	**88.2**	**94.7**	**95.5**	**79.8**	HC<AN<BN/mED
At least 3 FGID	**34.8**	**38.8**	**48.7**	**9.1**	HC<AN/BN<mED

Note: HC=healthy controls, AN=anorexia nervosa, BN=bulimia nervosa, mED=multiple eating disorders

In terms of overall FGID burden, experiencing three or more individual FGID was reported by 34.8-48.7% of individuals in the eating disorder groups compared with 9.1% of individuals in the healthy control group (q<0.05). Functional bowel disorders were the most commonly endorsed FGID category. In terms of specific FGID, IBS (43.9-58.8%) was the most frequently reported, followed by functional constipation (35.7-40.4%), and functional dyspepsia (23.4-31.1%) in the eating disorder groups.

All investigated disordered eating behaviors showed a strong positive association with most FGID categories (Table 9). Binge eating and purging showed a positive (statistically significant) association with all FGID categories, with the highest OR in the models between binge eating/purging and functional gastroduodenal disorders. Laxative misuse was significantly associated with all FGID categories, except for functional bowel disorders. However, it should be noted that confidence intervals were broad, most likely due to the small number of individuals endorsing laxative misuse. Fasting had the highest OR for functional gastroduodenal disorders, but it was also positively associated with functional esophageal disorders and functional anorectal disorders.

Table 9. Risk of functional gastrointestinal disorders (FGID) categories according to eating disordered behaviors. Presented here are results from logistic regression models: odds ratios (OR) with 95% confidence intervals. The models are adjusted for age, sex, and BMI. Q-values (p-values corrected for multiple comparison by FDR) are presented.

FGID	**ED behavior**			
	Binge eating ≥1/week (n=428)	**Purging ≥1/week (n=178)**	**Laxative misuse ≥1/week (n=32)**	**Fasting ≥6 days/month (n=239)**
A. Functional esophageal disorders	**2.0 (1.5; 2.7)** *(q< 0.001)*	**2.6 (1.9; 3.7)** *(q< 0.001)*	**3.5 (1.7; 7.2)** *(q= 0.001)*	**2.1 (1.5; 2.8)** *(q< 0.001)*
B. Functional gastroduodenal disorders	**3.3 (2.5; 4.3)** *(q< 0.001)*	**13.8 (9.6; 20.2)** *(q< 0.001)*	**3.6 (1.8; 7.5)** *(q< 0.001)*	**4.2 (3.2; 5.6)** *(q< 0.001)*
B. Functional gastroduodenal disorders (without Cyclic vomiting)	**2.5 (1.9; 3.3)** *(q< 0.001)*	**5.7 (4.2; 7.9)** *(q< 0.001)*	**4.4 (2.1; 9.1)** *(q< 0.001)*	3.5 (2.6; 4.6) *(q= 0.094)*
C. Functional bowel disorders	**2.3 (1.5; 3.7)** *(q= 0.001)*	**3.0 (1.7; 5.9)** *(q< 0.001)*	6.3 (1.3; 112.1) *(q= 0.094)*	1.5 (1.0; 2.4) *(q= 0.069)*
F. Functional anorectal disorders	**2.8 (2.1; 3.9)** *(q< 0.001)*	**2.9 (2.0; 4.0)** *(q< 0.001)*	**3.9 (1.9; 8.1)** *(q< 0.001)*	**2.3 (1.7; 3.2)** *(q< 0.001)*

Individuals with lower levels of current eating disorder symptoms (EDE-Q < 2.76) reported fewer FGIDs than individuals with higher symptom levels; however, they were still elevated above the healthy control referent group, suggesting that gastrointestinal disturbances persist even after reducing eating disorder symptoms (Figure 7).

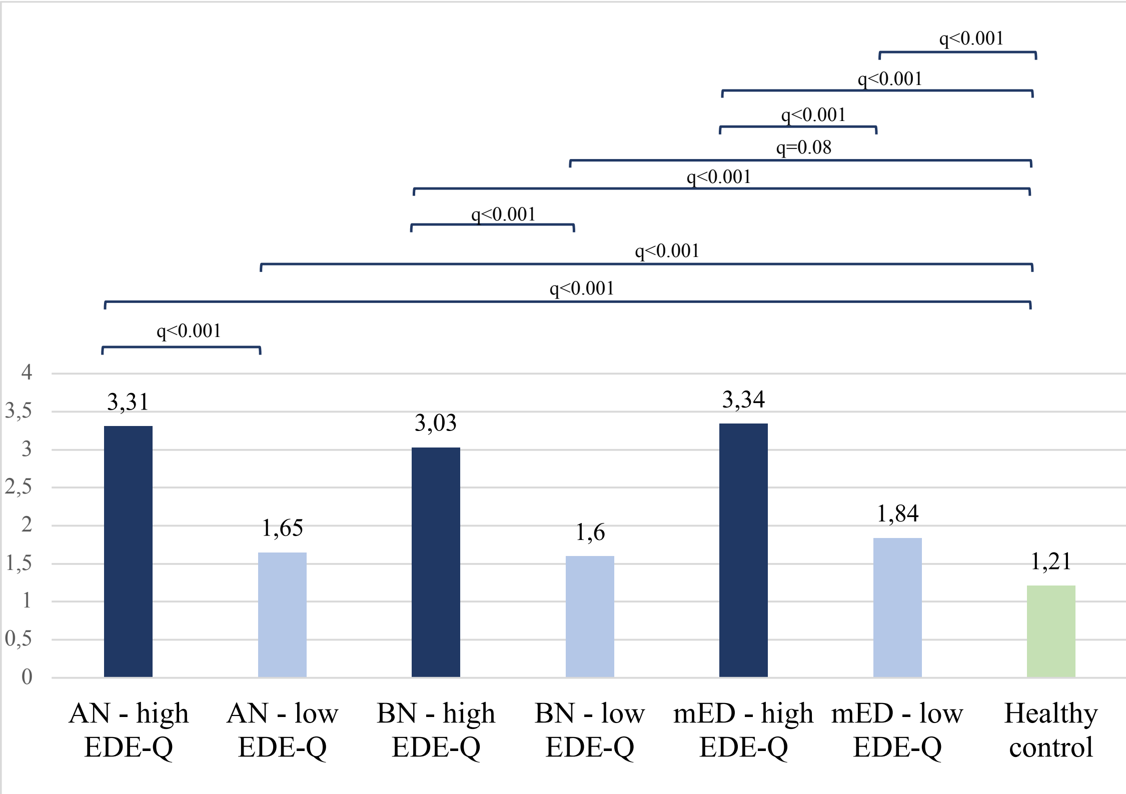

Figure 7. *Mean number of total FGID diagnosis in cases with low and high current ED symptoms and healthy controls. All groups with current high eating disorder symptoms had higher a higher mean number of total FGID compared to the groups with current low eating disorders symptom, and compared to controls (q<0.001). All groups with low current symptoms had higher mean number of FGID compared to controls, however the difference between the BN group and controls was not statistically significant (q=0.08).*

6.2 NUTRITION AND EATING DISORDERS

6.2.1 Intake of energy and nutrients and adherence to the Nordic Nutrition Recommendations in women and men with binge-type eating disorders (Study IV)

Objective

The objective of this study was to assess the dietary intake of women and men with binge-type eating disorders compared to healthy control subjects. In addition, we evaluated the participants' adherence to the recommended intake levels from the Nordic Nutrition Recommendation (NNR) in regards to energy, macro-, and micronutrients.

Main results

Women

The results showed that women with binge-type eating disorders had higher intake of total energy per day than controls (q<0.001). Additionally, their reported mean intake of energy per day is higher than the recommended level according to the NNR. Subsequently, only one in four of the female cases reported an energy intake within the recommended range.

The mean intakes for all macronutrients reached the recommended levels, except for too high intake levels of saturated fat and too low intake levels of omega-3-fatty acid, for both female cases and controls. For omega-3-fatty acids, in females, only 13.3% of cases and 9.5% of controls were within range, and there was no significant difference in adherence between the groups. Female cases had significantly lower intake of fat and protein, and significantly higher intake of carbohydrates than female controls; however, the absolute differences in intake were small and both groups achieved recommended levels. The mean intake of added sugar in both female cases and controls were within recommended levels; however, differences in adherence was large and statistically significant between cases and controls (64.2% vs 86%, q<0.001). A similar pattern, only reversed, was found for dietary fiber where mean intake of both cases and controls met recommendations, while adherence differed significantly between cases and controls (64.0% vs 44.3%, q<0.001).

In the case of micronutrients, the mean intake for female cases was lower than the recommended levels for vitamin D and higher than the recommendations for salt, which resulted in low adherence for those micronutrients. Only 10.4% (cases) and 6.8% (controls) were within recommended range for vitamin D (q=0.031). For salt, in women, 26.3% (cases) and 34.5% (controls) were within range (q=0.033). Compared to controls, female cases had significantly higher intakes of vitamins A, B_1, B_3, B_{12}, D, folate, magnesium, potassium, iron, copper, and salt, after adjusting for age and total energy intake per day. In the control group, women did not reach the recommended levels for folate, vitamin D, potassium, iron, selenium, copper, and salt.

Table 10. Recommendation levels of energy, macronutrients, and micronutrients according to the Nordic Nutrition Recommendations (NNR, 2012), mean and standard deviation (SD) in cases and controls, percentage of adherence to the recommendations in each group, for females and males separately.

Grouping of recommendations in the NNR	**Recommended level (NNR)**		**Cases**		**Controls**	
			Mean (SD)	% within NNR	Mean (SD)	% within NNR
Total energy (kcal)	Females	2000-2500§	2584.8 (1175.4)*	25.1*	2171.4 (858.3)	22.0
	Males	2500-3200§	2680.0 (1107.7)	20.0	2630.0 (883.3)	21.4
Fat						
Total fat (%E)	Females	25-40	31.9 (6.3)*	79.6*	33.1 (5.0)	87.6
	Males	25-40	31.5 (7.1)	70.0	32.7 (4.3)	85.7
Saturated fat (%E)	Females	≤10	12.1 (3.5)*	26.5*	12.5 (2.7)	13.2
	Males	≤10	11.9 (4.0)	34.9	12.8 (2.8)	21.4
Monounsaturated fat (%E)	Females	10-20	11.7 (2.7)*	73.0*	12.3 (2.1)	88.3
	Males	10-20	11.4 (3.0)	69.8	11.9 (1.3)	92.9
Polyunsaturated fat (%E)	Females	5-10	5.1 (1.5)	45.7	5.2 (1.1)	50.2
	Males	5-10	5.1 (1.4)	46.5	5.3 (1.4)	50.0
-n-3 (%E)	Females	≥1	0.6 (0.6)	13.3	0.5 (0.4)	9.5
	Males	≥1	0.6 (0.6)	18.6	0.5 (0.3)	7.7
Protein						
Total protein (%E)	Females	10-20	15.9 (3.6)*	89.8*	16.6 (2.7)	91.2
	Males	10-20	15.6 (3.6)	83.7	16.6 (1.5)	100
Carbohydrates						
Total carbohydrates (%E)	Females	45-60	49.2 (8.4)*	64.0	47.6 (6.5)	66.6
	Males	45-60	49.8 (8.9)	67.5	48.1 (5.0)	85.7
Sugar (%E)	Females	<10	9.0 (4.9)*	64.2*	7.1 (3.3)	86.0
	Males	<10	9.4 (5.9)	67.4	5.6 (2.0)	100
Dietary fiber (g/d)	Females	≥25	33.2 (21.5)*	64.0*	26.1 (12.9)	44.3
	Males	≥25	36.1 (24.9)	69.8	28.6 (10.7)	64.3

*Note: * indicates statistically significant difference between cases and controls at q<0.05*

Men

In this study mean total energy intake in men with binge-type eating disorders was within the recommended level; however, only 20% of case males reported an intake within the NNR range and 55% reported an intake above the recommendations.

The mean intakes reached the recommended levels for all macronutrients, except for saturated fat where intake was too high, and omega-3-fatty acid where intake was too low. Among males, 34.9% (cases) and 21.4% (controls) were in range for saturated fats. For omega-3-fatty acids, 18.6% (cases) and 7.7% (controls) were within range.

Table 11. Recommendation levels of vitamins according to the NNR, mean and standard deviation (SD) in cases and controls, percentage of adherence to the recommendations in each group, for females and males separately.

Grouping of recommendations in the NNR	Recommended level (NNR)		Cases		Controls	
			Mean (SD)	% within NNR	Mean (SD)	% within NNR
Vitamins						
Vitamin A (RE/d)	Females	700-3000	1060.9 (624.1)*	68.7*	860.8 (466.7)	55.5
	Males	900-3000	1026.4 (620.1)	53.5	892.4 (430.9)	50.0
Vitamin B_1/Thiamine (mg/d)	Females	≥1.1	1.5 (0.9)*	71.1*	1.4 (0.6)	61.0
	Males	≥1.4	1.7 (1.0)	60.5*	1.6 (0.6)	64.3
Vitamin B_2/ Riboflavin (mg/d)	Females	≥1.3	1.9 (1.1)	71.8	1.6 (0.8)	61.1
	Males	≥1.6	1.9 (1.1)	62.8	1.9 (0.7)	64.3
Vitamin B_3/Niacin (RE/d)	Females	≥15	43.2 (23.2)*	96.2	38.6 (16.4)	98.0
	Males	≥19	42.6 (22.0)	90.7	47.1 (16.4)	100
Vitamin B_6 (mg/d)	Females	≥1.2	2.2 (1.0)	84.4*	1.9 (0.7)	88.2
	Males	≥1.6	2.2 (1.1)	85.7	2.2 (0.6)	79.1
Folate (μg/d)	Females	400-1000	430.4 (214.6)*	47.4*	348.3 (157.7)	30.3
	Males	300-1000	443.4 (202.0)	76.7	351.9 (134.1)	64.3
Vitamin B_{12} (μg/d)	Females	≥2.0	4.6 (3.3)*	86.3	4.3 (2.4)	81.8
	Males	≥2.0	4.7 (3.0)	81.4	5.1 (2.0)	100
Vitamin C (mg/d)	Females	≥75	89.5 (52.2)	55.2*	80.3 (45.4)	48.5
	Males	≥75	91.3 (50.2)	51.2	76.3 (29.4)	50.0
Vitamin D (μg/d)	Females	≥10	5.5 (3.9)*	10.4*	5.3 (3.1)	6.8
	Males	≥10	6.1 (4.2)	11.6	5.9 (2.5)	14.3
Vitamin E (α-TE/d)	Females	≥8	14.8 (6.9)	82.7*	12.9 (5.4)	88.2
	Males	≥10	15.1 (6.9)	72.1	13.7 (4.6)	78.6

*Note: * indicates statistically significant difference between cases and controls at q<0.05*

In male cases, the mean intake did not reach the recommended levels for vitamin D (too low) and salt (too high), resulting in low adherence for those micronutrients. The mean intake of male controls did not reach the recommended levels for vitamin A and D, potassium, selenium, copper, and salt. Due to the small sample of male cases we did not analyze the difference between cases and controls.

Table 12. Recommendation levels of vitamins according to the NNR, mean and standard deviation (SD) in cases and controls, percentage of adherence to the recommendations in each group, for females and males separately.

Grouping of recommendations in the NNR	**Recommended level (NNR)**		**Cases**		**Controls**	
			Mean (SD)	% within NNR	Mean (SD)	% within NNR
Minerals						
Calcium Ca (mg/d)	Females	≥800	1107.6 (645.8)	66.6*	915.0 (470.0)	53.4
	Males	≥800	1113.1 (592.0)	67.4	1172.5 (506.5)	78.6
Phosphorus P (mg/d)	Females	≥600	1763.0 (905.6)	97.4	1524.3 (653.3)	98.2
	Males	≥600	1801.8 (859.6)	95.3	1829.8 (627.3)	100
Magnesium Mg (mg/d)	Females	≥280	476.9 (230.3)*	87.9*	391.3 (153.1)	77.7
	Males	≥350	498.6 (226.2)	74.4	440.3 (149.2)	78.6
Potassium K (mg/d)	Females	≥3100	3554.4 (1505.7)*	59.2*	3071.5(1111.0)	43.1
	Males	≥3500	42.6 (22.0)	90.7	47.1 (16.4)	100
Iron Fe (mg/d)	Females	≥15	15.1 (8.3)*	40.0*	12.5 (5.7)	25.2
	Males	≥9	15.8 (8.5)	83.7	13.8 (5.4)	85.7
Zinc Zn (mg/d)	Females	≥7	15.3 (8.2)	92.2	12.9 (5.6)	90.6
	Males	≥9	15.1 (7.2)	88.4	15.7 (5.3)	100
Selenium Se (µg/d)	Females	≥50	54.7 (32.6)	48.1*	48.8 (23.5)	40.2
	Males	≥60	57.3 (30.8)	37.2	51.6 (15.9)	21.4
Iodine I (µg/d)	Females	≥150	263.0 (135.7)	84.4	237.7 (105.6)	83.5
	Males	≥150	261.2 (106.1)	92.9	251.2 (85.5)	88.4
Copper Cu (mg/d)	Females	≥0.9	1.0 (0.6)*	53.1*	0.8 (0.4)	32.9
	Males	≥0.9	1.1 (0.5)	67.4	0.8 (0.3)	21.4
Salt/Na (g/d)	Females	≤6	8.5 (4.5)*	26.3*	7.7 (3.2)	34.5
	Males	≤6	8.6 (4.2)	23.3	9.3 (3.4)	0

*Note: * indicates statistically significant difference between cases and controls at q<0.05*

Sensitivity analysis

In a sensitivity analysis, we further explored the relationship between energy and macronutrient intake and number of binge-eating episodes by sub-categorizing the female cases into four groups with different frequencies of binge-eating (0, 1-4, 5-10, and >10 episodes) reported in the past 28 days (Figure 8 and 9). We found a non-significant difference in the daily energy intake and in the macronutrient intake between the group with no binge-eating episodes and the group reporting 1-4 episodes. In contrast, individuals in the two groups with higher binge-eating frequency, we found higher intake of energy and carbohydrates, and lower intake of fat. Only the group with the highest frequency of binge-eating episodes reported a significant difference in protein intake (lower).

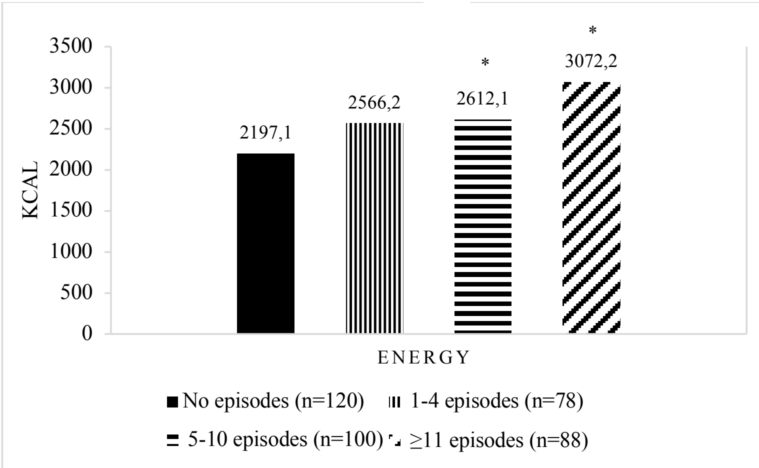

Figure 8. *Intake of energy (kcal) in female cases with different frequency in binge eating. The group with 5-10 and >10 binge-eating episodes had significantly higher mean intake of energy (*q<0.05).*

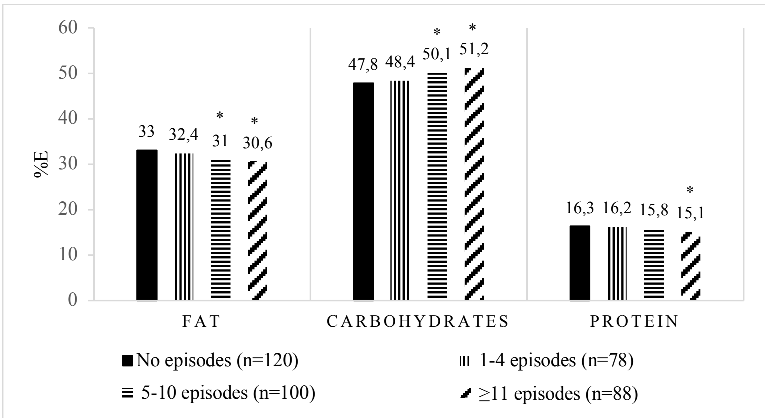

Figure 9. *Intake of macronutrients (%E) in female cases with different frequency in binge eating. The group with 5-10 and >10 binge-eating episodes had significantly higher intake of carbohydrates, and lower intake of fat. The group with >10 binge-eating episodes had significantly lower intake of protein (*q<0.05).*

7 DISCUSSION

7.1 MAIN FINDINGS AND IMPLICATIONS

The main findings from this thesis suggest that eating disorders are positively associated with both childhood BMI and gastrointestinal problems and that these relationships can partly be explained by genetic and familial factors. Further, functional gastrointestinal disorders co-occur with all types of eating disorders and correlate with symptom severity. Lastly, this thesis shows that women with binge-type eating disorders have an overall adequate diet, although their total energy intake is higher than recommended. Intake of nutrients was largely adequate; however, the thesis shows low general adherence to the recommended intake of essential micronutrients, such as vitamin D, iron, and folate.

7.1.1 Correlation between BMI and disordered eating

Study I revealed a positive correlation between BMI and disordered eating across childhood and adolescence and the correlation remained positive after controlling for later BMI. We further reported a positive genetic correlation between BMI at age 9/12 and age 15 and subsequent disordered eating indicating a longitudinal relationship between the two traits, which suggests that some of the same genetic factors may play a causal role in the development of both BMI and disordered eating.

These findings add to a large body of literature examining pre-morbid BMI in eating disorders.[65] Results from this study are both supported[60-62] and contradicted[63,64] by previous research; however, the longitudinal design and large sample, in combination with the genetically informative design, advances our understanding of the relationship. In addition, the results from this study are further supported by a previous twin study examining BMI in relation to EDI during the adolescent period, although only females were included.[167]

The design of Study I lends some clarity to the previous contradictory findings by showing that higher childhood BMI is positively correlated with increased risk of disordered eating in adolescence. However, this might not be true for all eating disorders. In Study I, disordered eating was measured using the EDI self-report scale, where individuals with AN have been found to score lower than individuals with BN, despite being seriously ill.[146] Their low scores could reflect several factors including the possibility that they actually do feel better when at low weight, denial of the seriousness of their condition, or low illness-awareness.[168,169] Underestimating the seriousness of disordered eating is common in patients with AN and has risen to be part of the diagnostic criteria in DSM-5.[169] Therefore, it should be considered that we might be capturing more of binge-type eating disorders (such as BN and BED) than AN, and that the positive phenotypic correlation between BMI and disordered eating conceals differential response patterns across eating disorder subtypes in the sample. A possible pathway for the positive association could be a combination of the genetic overlap between BMI and disordered eating, and an encouraging response to weight loss, from the surrounding environment (i.e., friends and family), in individuals who are overweight. Losing weight for someone who is overweight is unlikely to raise concern as it would have for a normal or underweight individual; however, a growing body of scientific literature[47,49,50,170] is suggesting that eating disorders in overweight and obese populations are largely overlooked and that it is crucial to increase awareness among both health care provider and parents that eating disorders can occur at any weight.

A previous study found different premorbid BMI trajectories in children who later develop eating disorders. Girls who later developed AN were significantly below the growth trajectory at age 4, as were boys who later developed AN by age 2, whereas girls who later developed BN were above the growth trajectory by age 2.[52] In girls and boys who later developed BED, the growth trajectories significantly diverged from controls at age 6. This observation is in line with new work in the genetics of AN that reported a bidirectional, causal, relationship between AN and BMI, further advancing our understanding of BMI as a part of AN etiology.[11,171] Currently, efforts are underway to collect large genetic samples of individuals with BN and BED and future studies will further enhance our understanding of the complex relationship between BMI and other eating disorders.[172]

In a similar vein, the results from Study I suggest that while elevated premorbid BMI may be a risk factor for later disordered eating, BMI is not only a consequence of eating disorders but may be an integral component of the disorders. The significant genetic correlations, based on a longitudinal model, suggest that some of the same genetic factors play a causal role for both BMI and eating disorders.[173] Specifically, future research should include the developmental period during adolescence to identify biological liability factors.

Focusing on clinical implications, the results of Study I and previous literature suggest that premorbid weight could be relevant to the etiology of eating disorders. Viewing childhood BMI in relation to age norms for those diverging both above and below expected values, in combination with screening for signs and symptoms of disordered eating, may assist in identifying individuals at particularly high risk of developing later eating disorders. Given that the child healthcare system in Sweden reaches >97% of all children age 0-5 years,[174] and that school healthcare is available in all schools, increased awareness and education around disordered eating behaviors in children and adolescents in the child- and school healthcare system could assist in early detection, and help prevent onset or halt disorder progression.

7.1.2 Gastrointestinal problems pre- and comorbid with eating disorders

Studies II and III both assessed different aspects of gastrointestinal problems and symptoms in relation to eating disorders. Both studies support the consistent evidence showing high prevalence of gastrointestinal complaints in eating disorders, and conversely, high prevalence of disordered eating behavior in populations with gastrointestinal disorders.[80,99,175] In Study II, we found those who reported current or previous long-term gastrointestinal complaints to have higher disordered eating, compared to those not reporting gastrointestinal problems. In addition, we investigated if the relationship was influenced by familial confounding and found the association between constipation and disordered eating behavior in adolescence to be attenuated, but still positive. Familial confounding refers to both genetic and environmental factors that are shared between the individuals in the twin pair that could account for the association. Examples of these factors could be shared genetic background (i.e., genetic factors influencing risk of gastrointestinal disorders), or environmental exposures (i.e., socioeconomic factors in the family or parental education), to which twins are equally exposed. The results indicate that the relationship between gastrointestinal problems and disordered eating is partly causal and partly due to familial confounding. In Study III we found that a considerable majority of individuals with an eating disorder reported at least one FGID, and almost half of the individuals reported three or more FGIDs. Further, all investigated disordered eating behaviors were strongly associated with most categories of FGID. Lastly, we showed that those with high current eating disorder symptoms had a higher mean number of FGIDs compared to those reporting low symptoms. Importantly, those with low levels of symptoms still reported a high mean number of FGIDs that controls without eating disorders.

The results of Study II converge with previous literature,[176] and extend existing knowledge by investigating the potential role of familial confounding factors. The familial confounding factors explaining part of the association between gastrointestinal complaints and disordered eating could be due to gene-environment correlations, which occur when genetic liabilities are expressed differently depending on the environment. For example, functional bloating (category C3 in the ROME III) could lead to a person being perceived as larger than desired, which for someone with a genetic predisposition to eating disorders might contribute to body dissatisfaction. This in combination with the societal thinness ideal could lead to disordered eating behaviors to control weight or shape.[177] Further, individuals with a history of gastrointestinal symptoms in childhood may develop heightened vigilance for gut sensations. This could contribute to increased risk for AN, for example through avoidance of uncomfortable gastrointestinal sensations by restricting food intake in order not to feel uncomfortably full.[177] In addition, childhood gastrointestinal complaints are often associated with food intolerances and allergies,[178] which are also associated with increased risk of both eating disorders and other psychiatric symptoms such as anxiety and depression.[179,180] Sensitivity to certain foods, in combination with avoidance of interoceptive sensation, might be part of the explanation for the association found between these phenotypes.

Several eating disorder behaviors also have strong associations with gastrointestinal complaints. An overall poor diet and inadequate nutrient intake in AN and BN is associated with constipation,[86] and constipation can also be caused by self-induced vomiting and misuse of laxatives leading to electrolyte disturbances and rebound constipation.[80,83] Furthermore, restrictive eating and fasting are predictors of postprandial fulness.[101]

The results from Study II and III add to the understanding of the complex and bidirectional relationship between gastrointestinal complaints and FGID and eating disorders, where symptoms of both phenotypes can potentially be mutually reinforcing. Furthermore, FGID criteria in some cases overlap with disordered eating behavior, such as postprandial distress syndrome where symptoms include feeling uncomfortably full after eating and not being able to finish a meal. It is difficult then to determine the direction of the relationship and it is most likely not a unidirectional, causal pathway.

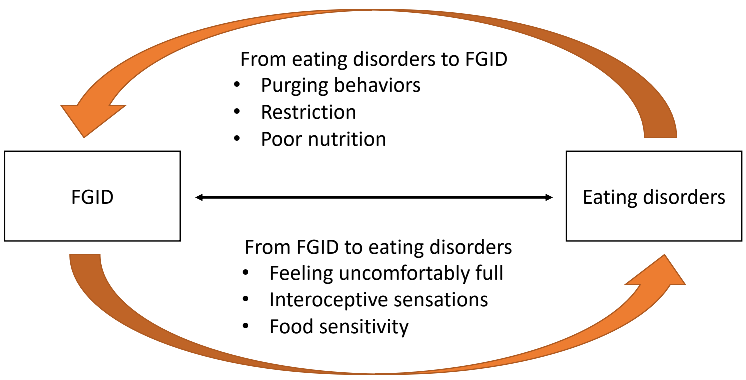

Figure 10. *Schematic illustrating a probable bidirectional relationship between FGID and eating disorders.*

Although gastrointestinal complaints are often reported to be reduced after treatment,[93,105] our results indicate that although the prevalence of total FGID burden is lower in those with low current symptomatology, compared to those with high symptomatology based on the EDE-Q, the mean number of individual FGID in low symptoms individuals than in the control group.

Due to the bidirectional relationship between gastrointestinal and eating disorders, longitudinal investigations across the course of illness and recovery are required to fully understand the temporality and causality of the relationship. In addition, future studies should investigate the role of persistent gastrointestinal complaints in risk of relapse of eating disorders. Clinicians treating patients with both eating disorders and FGID should be aware of the high co-occurrence of the two classes of disorders and the manner in which they may sustain each other. Adopting an integrated approach to treatment could prevent severe and chronic complications of this co-occurring pattern. Awareness of the comorbidity may help in developing treatment plans that manage such cases effectively and improve both mental and physical health, as well as ensuring long-term recovery of both illnesses.

Study II and III clearly showed that gastrointestinal problems and eating disorders are bidirectionally associated. The results further suggest a genetic component in the complex developmental pathway. Future research should explore underlying mechanisms that influence both classes of disorders in this relationship. Incorporating genetics into longitudinal clinical designs will allow us to further parse the impact of environmental and genetic factors on risk, maintenance, and outcome of this comorbid presentation.

7.1.3 Energy and nutrient intake in eating disorders

In Study IV, the energy and nutrient intake in individuals with binge-type eating disorders was evaluated and compared to healthy controls, and to the NNR. Overall, individuals with binge-type eating disorders were found to consume a diet adequately matching the recommended intake levels for most macro- and micronutrients. Unsurprisingly, in women, binge eating was positively associated with higher energy intake, and those with higher frequency of binge eating further reported a higher intake of carbohydrates, in relation to other macronutrients, compared to those reporting lower frequencies of binge eating. Study IV is the largest evaluation of dietary intake in women with binge-type eating disorders to date. Despite the fact that eating is the central symptoms for these disorders, actual nutrient intake has been understudied. Previous studies have involved small select samples leaving many open questions about nutrient intake in these disorders.[181]

Women with binge-type eating disorders not only report higher total energy intake compared to controls, but also higher energy intake relative to the reference intake by the NNR. In addition to the mean energy intake being above recommendations, a large proportion of the individuals with binge-type eating disorders (42%) reported energy intake above the recommended range. Previous research has also shown that individuals with binge-type eating disorders underreport caloric intake, suggesting that the actual mean intake in this sample might be even higher.[113,128] An excessive intake of energy compared to energy expenditure is associated with weight gain, possibly contributing to the development of overweight and obesity, as well as related comorbidities such as hypertension, type 2 diabetes, and coronary disease.[138,182] Previous literature has shown that women with BN are at higher lifetime risk of cardiovascular disease.[183] Our sample was currently too young to evaluate cardiovascular outcomes (mean age 28.3 years), we have permission to follow-up participants as they traverse the age of risk for these conditions.

Overall adherence to macronutrients was adequate in women with binge-type eating disorders. However, the results show low adherence to limiting sugar in the diet, suggesting that individuals with binge-type eating disorders consume foods with sugar to a greater extent than controls. In contrast, a higher proportion of women with binge-type eating disorders reached the recommended intake of fiber (found in whole grains, fruits, and vegetables) compared to controls. Individuals with eating disorders have been found to have a higher intake of fiber compared to controls in previous research as well.[110] This finding may indicate that individuals with eating disorders, despite having disordered eating behaviors, may also attend to fiber intake, possibly even to ensure regularity to limit gastrointestinal discomfort documented in the other studies presented in this thesis. We did not query the "why" behind food intake, which would require more detailed qualitative methodology.

Adherence to micronutrient recommendations aligned with previous literature showing adequate intake for most nutrients, with the exception of insufficient intake of vitamin D, excess intake of salt, and a low proportion of individuals reaching recommendations for intake of iron and folate. The low adherence to folate and iron recommendations was observed in both female cases and controls and is of considerable concern as a large portion of the women in this sample are in their reproductive years. Eating disorders are known to be associated with obstetric and gynecological problems.[184] For example, binge eating has been associated with amenorrhea and oligomenorrhea even after controlling for BMI, polycystic ovary syndrome, and age.[173] The results of Study IV underscore the importance of adequate prenatal care for individuals with binge-type eating disorders to ensure that their diet is adequate in nutrients essential for healthy pregnancy outcomes. That controls also had inadequate intake of these micronutrients suggests the need for greater education regarding nutritional requirements for women in this age range—especially those intending to reproduce.

In Study IV, the sample of male participants was too small to perform between-group comparisons. Descriptively, males on average met nutrient recommendations, but the mean intake of energy was unexpectedly low considering that the males in the sample were to a large extent actively ill and a majority of the male cases reported having one or more binge-eating episodes per week (56%). The sensitivity analysis showed a positive association between frequency of binge eating and energy intake, and we would therefore expect males to have a higher total mean intake of energy. However, the limited sample of males in Study IV hindered us from conducting sensitivity analyses, and future research should explore the energy and nutrient intake in males with eating disorders as this is a group is underrepresented in research.

Study IV used a validated method for recording diet; however, results should be confirmed in future studies using other methods of measuring dietary intake such as a 4-day food diary where intake measurements are recorded prospectively and where participants can report differences between normal meals and binge-eating episodes in regard to energy and nutrient content, and frequency.

In terms of clinical implications, the fact that individuals with binge-type eating disorders fell short of certain nutrients and had excessive energy intake suggests a greater need for attention towards ensuring that particular aspects of daily intake meet recommendations. Addressing dietary intake is a delicate topic in the treatment of binge-type eating disorders and requires careful training of dietitians. Untrained dietitians or dietitians who are unaware of an individual's eating disorder history could prescribe caloric restriction for weight loss that could perpetuate or re-ignite binge eating. Results from this study provide a valuable backdrop for understanding eating patterns in eating disorders and can aid dietitians in evaluating and prescribing nutritional changes that achieve recommendations but do not encourage risky restriction.

Despite the central role diet quality, dietary patterns, and energy balance play in eating disorders, this study is one of the first large, well-controlled studied assessing actual nutrient intake. Characterizing eating patterns in individuals with different eating disorders is valuable for the development of more empirically based nutrition counseling, especially focusing on lasting health benefits beyond the initial treatment of the eating disorder.

7.2 METHODOLOGICAL CONSIDERATIONS

7.2.1 Measures

This section discusses measurement issues across the four included studies. The questions regarding gastrointestinal problems in Study II have not been formally validated, meaning that we cannot be sure that the questions are measuring what they are supposed to measure. Ideally, a more in-depth and validated instrument would have been used, such as the ROME IV FGID for children and adolescents, particularly since FGID in childhood are associated with later adult FGID.[71,72] Additionally, the questions regarding gastrointestinal problems were reported retrospectively and phrased in a manner that captured the entire childhood period up until the time of assessment. We were therefore unable to establish a timeline for when gastrointestinal problems and disordered eating symptoms first occurred, and in what order. However, the two time points of evaluating gastrointestinal problems in Study II (at age 9/12 and at age 15) suggest that the observed association either reflects a difference between parent-report and self-report, or a difference in age of onset of gastrointestinal problems. The self-reported measures at age 15 may to a larger extent reflect gastrointestinal problems that are current or that have their onset closer in time to the assessment point. In contrast, the parent-reported measures of symptoms at age 9/12 may reflect more early childhood problems. Since we do not see an association between gastrointestinal problems at age 9/12 and disordered eating, there may be a critical window during which gastrointestinal problems are associated with eating disorders. Longitudinal studies with prospective, rather than retrospective, design with detailed measures, could help to clarify the issue of timing.

All included studies used self-reported instruments to capture eating disorders symptoms and behaviors. Although all included measures have been validated (EDI[146], ED100K[149], and EDE-Q[152]), there are limitations to using self-reported data. Previous research has found that individuals with AN score lower than patients with BN on self-rating scales, even when severely ill.[146,147,185] This has been explained by low sickness-awareness (i.e., anosognosia) or could reflect that individuals with AN do report feeling better when they are at low weight. However, with the emerging evidence from genetic research showing shared underlying genetic components between AN and low BMI, it might be that for some patients it is not low sickness-awareness causing the low scores, but rather the instruments that are not able to capture underlying biologic mechanisms that drive the eating disorder. Thus for example, those individuals who score low on the drive for thinness scale of the EDI might not be in denial of their symptoms, but rather they may have a variant of illness that is driven more by genetic liability for low BMI or other as of yet undescribed metabolic factors.

In addition, accurate assessment of binge-eating episodes can be challenging when using self-reported measures.[186,187] A binge-eating episode is defined as eating an unusually large amount, in a specific amount of time (such as for example a two hour period), combined with having a sense of loss of control over the eating. A previous study found an overestimation of the frequency of binge-eating episodes when comparing self-report (EDE-Q) to interview (Eating

Disorders Examination, EDE). Frequency of binge eating was the variable used to assess the association between FGID and eating disorder behavior in Study III, and in the to assess the association with energy and macronutrients in the sensitivity analysis of Study IV. If the frequency of binge-eating episodes was overestimated, the associations would have been underestimated in the analysis. However, the conclusions of either Study III or IV would have been unlikely to change.

In Study IV, the FFQ MiniMeal-Q was used to collect data on energy and nutrient intake. Although we used a validated assessment tool for the dietary data collection, accurate measurement of food intake is extremely challenging. The accuracy of retrospective reporting of food intake relies on the respondent's memory. In general, when individuals report dietary habits, unhealthy foods tend to be under-reported, whereas healthy foods are over-reported. Previous research has found underreporting of energy intake to be associated with elevated BMI and overweight.[188,189] In addition, underreporting of energy has specifically been associated in individuals who are both overweight and have a desire to lose weight.[190] Moreover, males are more likely to underreport energy intake than females[189] and younger people, compared to older people, are more likely to underreport energy intake.[191] Furthermore, women with BED have been found to underreport their energy intake to a greater extent than controls.[128] In light of these factors, the result concerning the unexpectedly low energy intake in male cases might be explained considering that the group is both overweight, male, and has active binge-eating behavior. Given these challenges in measuring dietary intake, future efforts should be made to replicate the results found in Study IV, using different dietary assessment methods.

Weight and height were collected using parent and self-report in CATSS and by self-report in BEGIN-SE. Research has shown that weight reported online and objectively reported weight are highly correlated; online reporting is a valid method of data collection in both the general population[192] and in individuals with eating disorders.[193-195]

7.2.2 Validity and generalizability

The validity and generalizability of studies is dependent on the ability to replicate studies and reproduce the findings. In Study II, and III we were able to reproduce and extend findings from previous literature in larger samples than previously studied. This increases the validity of our results and facilitates in the interpretation of the findings. In Study I, our results were both in agreement with and in contrast to previous studies on the topic reflecting the complex role that BMI plays in eating disorders. However, the results from Study I enhance knowledge in the field due to the large sample size and a prospective longitudinal design. The large sample size in Study I and II also contributes to increased reliability as it increases the precision in the estimate and reduces uncertainty. The sample size in Study III and IV was smaller, but data on both exposures and outcomes were more detailed than in Study I and II, which improves precision and sub-classification of symptoms. Although the results from Study IV to some extent reproduced existing findings in the field, the study requires further replication using other methodologies.

Although it is sometimes argued that twins are different than the general population, either because they are more often born prematurely or they are treated differently by virtue of being twins, this has very little support in research.[196,197] Twins have been found to be comparable to singletons on most parameters measured supporting the generalizability of the results of Study I and II to singleton populations.

In Study III and IV, the individuals who participated in the study were a slightly selected group as they were individuals with eating disorders who had sought treatment at a specialized treatment clinic somewhere in Sweden. Treatment-seeking individuals with eating disorders may not be representative of the general eating disorders population, and in addition we know that many individuals are reluctant to seek treatment and that the duration of illness prior to seeking treatment has been reported to range from 53 to 67.4 months.[198] Accordingly, this should be considered when evaluating the generalizability of our results to the eating disorder population as a whole.

7.2.3 Methods

Twin designs have considerable advantages to explore the relationship between genes and environment in different phenotypes without having measured actual genetic variants. However, the models rely on several assumptions and carry possible limitations.

One of the major critiques of twin studies is the reliance on the Equal Environments Assumption (EEA). The EEA holds that MZ and DZ twins share their shared environment (the C component in the twin model) to an equal extent. If this is not true, and assuming that MZ twins share more of their environment, this could potentially increase the importance of the A component (the additive genetic effect) in a twin model. Although it might be expected that the shared environment is not actually the same between MZ and DZ twins in terms of for example parenting and bond between the twins, previous research testing the EEA in psychiatric disorders (including bulimia) has found the assumption to be valid.[199]

Another assumption in twin modelling is the assumption of no strong effects of assortative mating.[42] Meaning that people choose a mate randomly and not choose someone who is phenotypically more similar or dissimilar to themselves. This assumption has been shown to hold to different extents depending on the trait of interest, and within, and across, psychiatric populations evidence of non-random mating has been found.[200] Over time, non-random mating will cause an underestimation of heritability, but it is unlikely that such effects would have greatly influenced the findings of this thesis given the high heritability estimates found for disordered eating at all ages in Study I.

A potential issue with the within-twin pair analysis is that only twins who are differentially exposed to gastrointestinal problems contribute to the estimation of the regression coefficient in the conditioned linear regression analysis. This dramatically limits the sample size, and therefore reduces the ability to detect potential associations. Furthermore, we should consider the possibility that unmeasured factors that cause the twins to be differentially exposed, and that those factors could possibly lead to different outcomes.[158] In addition, the within-twin pair design assumes there is no sibling contagion effect or carry-over effect,[201] meaning that neither the exposure nor the outcome in one twin influences the outcome in the other twin. It is unlikely that gastrointestinal problems in one twin would directly cause disordered eating in the other twin; however, it is possible that disordered eating in one twin might directly influence disordered eating in the other twin. If so, the association would be underestimated in the analysis[202] but most likely not change the conclusion of Study II.

A major concern in case-control studies, like Study III and IV, is selection bias. Selection bias occurs if the association between the exposure and the outcome differs between those who participate in the study compared to those who do not. For example, if potential controls who have more problems with gastrointestinal complaints participate in the study and potential controls who have no gastrointestinal complaints do not participate in the study, the estimated OR would be reduced. In the BEGIN-SE study, the primary focus is on genetics and microbiome research, therefore the likelihood of participating could possibly be influenced by a potential participant having a specific interest in those research areas. Further, some individuals, both cases and controls, declined participation due to reluctance to provide stool samples. Selection biased by the willingness to provide a stool sample could introduce unknown bias to our findings. Selection bias can for the most part only be assumed, as the association between exposure and outcome in non-participants is unknown.

7.3 ETHICAL CONSIDERATIONS

The work presented in this thesis originated from data collected using interviews and questionnaires in the two studies CATSS and BEGIN-SE. The data collection for the two studies was planned so as to reduce participant burden. For example, the questionnaires are online and smartphone-friendly so they can be completed conveniently. Although many surveys and questionnaires are included in both studies, great care was taken to only include sections relevant to the original research questions. Individuals participating in the studies were informed that their participation in the studies was voluntary and could be ended at any time.

In the CATSS study, all participants provided informed consent prior to entering the study. The participants are regularly given the option to withdraw their consent and discontinue participation. CATSS is a population-based cohort study in which the participants are not targeted because of a particular outcome, and are then followed over time. The data collected in CATSS are either via telephone interview or online questionnaires. This type of study carries minimal risk for the study participant. CATSS has been approved by the Regional Ethical Review Board in Stockholm, Sweden (Dnr: 02-289, 2010/597-31/1).

In the BEGIN-SE study, all participants give informed consent before entering the study, and are informed that they can leave the study at any point without having to give a reason. It is of particular ethical importance that when conducting research in a patient population to inform and reassure participants that their treatment is in no way connected to the research. The participants' enrollment, decline, or drop-out from the research study does not affect their treatment in any way. The BEGIN-SE study has been approved by the Regional Ethical Review Board in Stockholm, Sweden (Dnr: 2013/112/31-2, 2016/1852-32, 2017/40-32).

Another ethical consideration in this thesis is the risk of stigmatization. Although efforts have been made to reduce stigma and increase awareness around eating disorders[1], stigma and shame are still among the most prominent perceived barriers towards help-seeking.[203] Ethical considerations pertain to how the results are presented, and in what way they may be perceived and interpreted. Especially, the issue of explaining increased genetic risk and liability has the potential to be misinterpreted as genetic determinism.[204] Care regarding interpretation and dissemination of results must be taken, both in regard to the research community and to the general population.

The knowledge gained from these projects is expected to provide significantly increased understanding of the underlying biological and environmental factors in eating disorders, with both direct and indirect implications for prevention and treatment. This is expected to far outweigh the potential risk that the participants might face.

Data collection and handling

Data from both CATSS/the Swedish Twin Registry and BEGIN-SE are pseudonymized, and researchers only access data with serial numbers for analysis. The code keys are kept by the principal investigators for each respective project. Those responsible for data management at the Karolinska Institutet have extensive experience in administrating personal data materials, and data handling followed recommendations for good practice in data management and stipulated within the Personal Data Act in Sweden (Swedish abbreviation: PUL) and with the European General Data Protection Regulation (GDPR).

Therefore, no individuals could be identified through the work of this thesis. By ensuring that data was handled in a proper way, and that only limited data were available when the data were analyzed, the risk of identification through back tracking was minimized.

8 CONCLUSION

The work presented in this thesis provides insight and knowledge regarding several aspects of factors influencing the emergence and maintenance of eating disorders.

Study I enhances the understanding of the positive association between BMI and eating disorders during the developmental period and shows a partially overlapping genetic component between the two traits.

Study II demonstrates that eating disorders are positively associated with gastrointestinal problems across childhood and adolescence and that the relationships can be accounted for by genetic and familial factors.

Study III evaluates and confirms the high co-occurrence of FGID with all types of eating disorders and with disordered eating behaviors, and shows a positive correlation between gastrointestinal problems and eating disorder symptom severity.

Lastly, Study IV shows that women with binge-type eating disorders have an overall adequate nutritional intake compared to the NNR, although they have a total energy intake that is higher than recommended, and fall short in certain nutrients. Further, binge-eating frequency is positively associated with higher energy intake and with increased intake of carbohydrates.

9 ACKNOWLEDGEMENTS

These past years have been some of the most rewarding and enjoyable, but also challenging, of my working life. I would like to thank a number of people who have contributed and supported me during these past five years to make this thesis possible.

First of all, I would like to thank all the participants of the **CATSS** and **BEGIN-SE** studies. Without people taking time out from their lives to participate in research and share their experience, we would not be able to continue to answer research questions with the aim of improving health and life for future generations. Thank you!

I have been fortunate to have a team of supervisors, all with extensive skills and knowledge in their respective fields to help me through these past years. First and foremost, I would like to thank my main supervisor **Cynthia Bulik**, I am forever grateful for all the guidance, support, and encouragement you have given me during these years, and for giving me the opportunity to do this thesis. Despite your busy schedule, you always make time for meetings and to answer question, big or small. Your passion for science and research is inspiring!

To **Ralf Kuja-Halkola**, thank you for all hours you have spent *explaining* things to me. Thank you for being so generous with your time and knowledge in statistics – I have felt extremely lucky to have you as a co-supervisor on this journey.

To **Elisabeth Welch**, thank you for your open-door policy and for always having a moment to talk to me. Thank you for inviting me to have an office at SCÄ, it was some of the most rewarding days of my PhD.

To **Katarina Bälter**, thank you for taking me on as your master student in 2014 and for introducing me to MEB. Thank you for agreeing to be my co-supervisor for this PhD period and sharing your expertise in nutrition epidemiology.

To **Paul Lichtenstein**, thank you for agreeing to be my co-supervisor and for the tremendous work creating the CATSS study. In addition, thank you for the constant support you show the PhD students at MEB, first during your time as head of department and now as the study director.

To **Laura Thornton**, my co-author and informal mentor, I don't even know where to start to describe my admiration and gratefulness to you. Not only are you generous with your time, extensive(!) knowledge, and guidance, you are also a kind person who truly care about others, and I am so grateful that you invited me and my family to your home and into your life.

To **Anne-Marie Boström**, my external mentor, I am so happy and thankful for all the cheerful support and fun lunches at Svarta Räfven we have shared over the years. You are such a generous person and a true go-getter and I hope you will agree to continue our lunch tradition even when I am not a PhD student anymore.

It has been a privilege to be part of such a friendly and excellent research group at the **Centre for Eating Disorders Innovation, CEDI**. Thank you to **Cindy** and **Bengt Fundin** for providing great leadership and a stimulating work environment. To all members of CEDI throughout the years, thank you for creating a warm and inspiring environment to work in, I have really enjoyed working with, and learning from, all of you. Including, but not limited to: **Johan Zvrskovec Källberg, Jessica Pege, Chris Hübel, Malin Rådström, Virpi Leppä, Afrouz Abbaspour, Britt-Marie Hune, Peter Lind, Annelie Billger, Andri Savva, Marianna Rania, Maria Seidel, Andreas Birgegård, Emma Forsén Mantilla, Elin Monell, Johanna Levallius, David Clinton, Ruyue Zhang, Stina Borg, and Jet Termorshuizen**. To **Andreas Jangmo**, for being one of the first people at CEDI, for the conference memories and many coffee breaks, and for being a friend, thank you. To **Lauren Breithaupt**, you are the most intelligent and hard-working person I know, thank you for your friendship and constant encouragement even when we are separated by an ocean.

A special thank you to **Andreas, Emma, and Afrouz**, for so generously helping me with my kappa.

To my **SCÄ FoU** friends, I enjoyed so much being a part of your work group, thank you for making me feel welcome and for delicious Friday fika: **Marie Carp, Kristofer Ekström, Anne-Charlotte Wiberg, Anja Levin, Lisa Brask**, and more.

MEB is a fantastic department and a great place to work. In particular, I would like to thank **Alessandra Nanni, Janina Mahmoudi, Gunilla Nilsson Roos, Gunilla Sonnebring, and Marie Jansson** who have been especially helpful and kind whenever I have needed their administrative help during these years.

To MEB PhD students and colleagues (past and present), including but not limited to: **Shuyang Yao, Isabelle Brikell, Camilla Sjörs, Anna Plym, Carolyn Cesta, Anna Hedman, Laura Girardi, Elisa Longinetti, Mina Rosenqvist, Mark Taylor, Frida Lundberg,** and many more. Thank you all for creating such a collaborative and great research environment.

To my friends outside work (well, not completely), thank you for filling my life with friendship and ensuring me that there is more to life than work. To **Amalia and Erika**, thank you for

growing up side-by-side with me for the past 20 years, it is a privilege to have such loyal and lovely friends. To **Tova**, thank you for friendship and encouragement, and for always making up plans for the future, even if they keep getting cancelled. To **Louise**, the best that Skåne has to offer! I value our friendship high and am so glad we are remote colleagues. To **Nora**, for emotional support and friendship during PhD life, family life, and beyond, thank you. To **Lotfi**, thank you for long-lasting friendship, and for discussions about research and life.

To my extended family, the **Wiklunds**, thank you for making me feel welcome in your home and in your family from day one. To **Ingela**, you are a true inspiration to me. As a woman, as a researcher, and as a mother. Thank you for all our conversations throughout the years, about life and about science. I could not have asked for a better mother in law.

Thank you to my family for unconditional love, support, and encouragement. To my big brothers, **Johan and Edde**, thank you for being great role models in following your dreams. Especially thank you to my parents, **Micke and Maria**, for giving me the greatest gift in life, the confidence to believe I can do anything.

To **Love and Wilma**, thank you for reminding me every day of what is most important. You are everything!

Johannes, clear eyes, full heart, can't lose. I love you forever.

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